EXPERT REPORT OF MARK A. SCHUMACHER, M.D., Ph.D.

MARCH 25, 2019

TABLE OF CONTENTS

I. INTRODUCTION

1. My name is Mark A. Schumacher, M.D., Ph.D. I have been retained by Plaintiffs Cuyahoga County and Summit County to offer my expert opinions on issues related to the medical use of opioids for the treatment of pain, the conduct of opioid manufacturers relating to the marketing and promotion of prescription opioids, and related topics.

2. My curriculum vitae, a copy of which is attached as **Appendix 1** to this report, describes my education, background, qualifications, and my publications. I have not testified in deposition or at trial in the last four years.

3. I am being compensated at a rate of $450 per hour for my services in this litigation. I am also being reimbursed for all reasonable expenses incurred for my work on this litigation. No part of my compensation is contingent upon the outcome of this litigation, and I have no interest in the litigation or with either party.

4. This report contains a true and accurate statement of my opinions in this matter. The matters cited in this expert report are based on my personal knowledge, education, and years of medical experience and, if called to testify, I will testify to the same effect. These opinions are based on my education, training and experience as well as the data, evidence, and literature cited herein and are offered to a reasonable degree of medical certainty. I reserve the right to supplement my analysis and opinions based on additional evidence or information that is made available to me after the date of this report, including additional expert disclosures made after March 25, 2019, as approved by the Court.

II. SUMMARY OF OPINIONS:

5. It is my opinion, based on my expertise in the field of pain management, that the increased prescribing of opioids in the United States has caused tremendous harm that would not have occurred if not for the actions of the companies that aggressively promoted the use of

opioids for a wide array of conditions beyond short-term acute pain, cancer pain from active disease, and end-of-life and hospice care.

6. The prevalence of chronic pain is a valid concern but should not be confused with underutilization of opioids. In addition, to the extent that there was some amount of under-treated pain, it does not follow that the best treatment then (or now) would have been an opioid; indeed, in the vast majority of cases the best treatment would have been something other than an opioid, and likely a combination of physical, pharmacologic, and behavioral approaches.

7. More specifically, I provide the following opinions based on my experience, review of academic literature, and review of documents and certain information produced in discovery in this action:

8. It is my opinion to a reasonable degree of certainty in the field of pain medicine that the medical standard of care for treating both chronic and acute pain was changed as a result of widespread promotion and marketing of opioids by Defendants[1] that trivialized the risk of addiction and exaggerated the benefits of long-term opioid use.

9. It is my opinion to a reasonable degree of certainty in the field of pain medicine that Defendants influenced physicians through direct-to-physician marketing, medical education, and industry-sponsored and -funded Key Opinion Leaders ("KOLs") to prescribe long-term opioids based on misinformation about the risks and benefits of chronic opioid use.

10. It is my opinion to a reasonable degree of certainty in the field of pain medicine that for the vast majority of chronic pain patients, the risks of prescription opioids significantly

[1] "Defendants" as used herein refers to the Defendant manufacturers of branded and generic opioid products in the actions brought by Plaintiffs Cuyahoga County and Summit County: Purdue Pharma, Endo, Janssen, Teva, Cephalon, Mallinckrodt, Actavis, and Allergan.

outweigh any benefits, and that at most, a small percentage of chronic pain patients achieve meaningful relief from the long-term use of opioids.

11. It is my opinion to a reasonable degree of certainty in the field of pain medicine that even for those indications for which opioids are effective, such as trauma or post-operative pain, the risks of prescribing opioids are significant such that non-opioid alternatives or multimodal analgesia should be used whenever possible to reduce opioid use.

III. BACKGROUND

A. General qualifications and background

12. I am a Professor and Chief of the Division of Pain Medicine in the Department of Anesthesia and Perioperative Care, University of California, San Francisco (UCSF). My education and training include a PhD (Physiology and Pharmacology) and M.D. at the University of California, San Diego. Following an internal medicine internship at Cedars Sinai Medical Center, I completed a residency in anesthesiology at UCSF and devoted my academic career to advance pain medicine through clinical care, teaching and research. I advanced Clinical Pain care at UCSF through the introduction of low-dose ketamine, a non-opioid analgesic adjunct that decreases opioid tolerance, opioid requirements and reduces hyperalgesia (Anesthesia & Analgesia 2001); introduced multimodal analgesia for orthopedic joint surgery to minimize opioids and enhance early mobilization and discharge; served as Director of UCSF Pain Services 2010-2015 and am currently serving as Chief of Pain Medicine since 2010; and directed three UCSF Pain Summits (2011, 2013, 2015). I also served on the National Academies of Sciences, Engineering, and Medicine, Committee on Pain Management and Regulatory Strategies to Address Prescription Opioid Abuse - Consensus Report, July 2017: "Pain Management and the Opioid Epidemic" (R. Bonnie 2017).

13. As part of my teaching responsibilities, I have instructed medical students (Anesthesia 110) residents and fellows in pain management; served as Director of the NIH Center of Excellence in Pain Education at UCSF; and co-authored a chapter on "Opioid Analgesics & Antagonists" in Katzung's *Basic and Clinical Pharmacology* 8th – 14th edition. My original research on pain includes, as co-author, isolation and characterization of the Capsaicin Receptor TRPV1 (Caterina et al. 1997), a break-through in identifying a novel pain receptor and non-opioid analgesic target; and more recently, identifying Transcription Factor Sp4 as being required for hyperalgesic persistence (Sheehan et al. 2019), proposed as a novel target to block the transition from acute to chronic pain.

14. I became concerned with bad outcomes resulting from chronic use of opioids in the early 2000s within my own teaching hospital as I became aware of opioid-induced respiratory failure and/or lack of analgesic response in patients administered various formulations and doses of opioids. One of the most dramatic concepts was the idea, promoted at the time, that one could achieve effective analgesia for any pain problem by simply increasing the dose, strength and/or frequency of an opioid to overcome a patient's complaint of severe pain over time. As an example, an unfortunate young woman had developed graft versus host disease following a bone marrow transplant resulting in a progressive sloughing (desquamation) of her skin (80% burn) and enteral lining leading to severe pain plus extensive GI bleeding. The administration of increasing doses and infusions of fentanyl over several weeks, despite continued complaints of 10+/10 pain, resulted in her receiving the unimaginable doses of 3.4 liters of fentanyl per day. In fact, her pain appeared to be getting worse instead of better despite the enormous doses of fentanyl (Eilers et al. 2001). Fortunately, with the addition of the analgesic adjunct low-dose ketamine, that had not previously been used in our institution for the

potential treatment of opioid tolerance and hyperalgesia, we were able to reverse this life-threatening direction and wean off the fentanyl, achieve analgesia and discharge her from the ICU (Eilers et al. 2001).

15. This outcome seemed at odds with the idea of opioids having no ceiling effect. More broadly, I began to examine the marketing about the purported opioid efficacy and low risk of addiction with the use of long-term opioid use and OxyContin. My studying the issue, and figuring out how to deal with it, prompted me to question what had become the status quo—and not just for chronic pain, but how we were managing opioid-naïve patients entering the hospital for elective joint replacement and many leaving on long-term opioids including OxyContin. Because many in the medical community, including myself, were persuaded at the time that opioids were safe and effective for long-term use, there was less concern about providing 30 or even 60-day supplies for acute injuries / post-operative recoveries. Overall, many physicians at the time, having been persuaded that opioids were safe if used as prescribed, believed patients would use what they needed and no more, and therefore having extra was not a problem. At some level, longer discharge prescriptions also reduced the need for doctors to schedule follow-up visits for refills. As the decade progressed and I engaged in a number of educational and operational initiatives to improve the safety of opioid use in the hospital, I also engaged in programs to reduce the burden of opioids through the introduction of multimodal analgesia to reduce the prescription of opioids during and upon discharge. I was especially struck by a paper published by Dr. Susan Okie in 2010, "A Flood of Opioids, a Rising Tide of Deaths" (Okie 2010), which succinctly presented the tragic consequences of unintended overdose and death from prescription opioids.

16. The Okie paper motivated me to do more at my institution in this area, including directing multiple "UCSF Pain Summits" and other educational efforts to trainees and physicians.

B. Understanding the Biology of Opioids and Pain

1. What is an opioid?

17. Opioids are compounds that work at opioid receptors in the central and peripheral nervous system that are involved in modulating the sensation and perception of pain. These include opiates: naturally occurring alkaloids found in opium, including morphine, codeine, thebaine, and papaverine. Opioids also include synthetic and semi-synthetic compounds often with potencies greater than morphine. Whether naturally occurring in the opium poppy or fully synthesized in a chemist's laboratory, all of these opioids are classified as "exogenous opioids"—external to the body. There are also "endogenous opioids," which occur within the body. The most commonly known group of endogenous opioid peptides are the endorphins. Popular culture descriptions of a "runner's high" or "endorphin-boosting exercises" refer to the body's own opioid system, which is critical to many bodily functions. When people take exogenous opioids—whether Vicodin (hydrocodone), morphine or heroin—they are consuming a substance that fits into the body's own analgesic system like a progressively oiled key in a lock.

18. Depending on their intrinsic activity or efficacy, opioids may be classified as full agonist, partial agonists, and antagonists. The receptor-activating properties and affinities of opioid analgesics can be manipulated by pharmaceutical chemistry to make them more or less potent, and depending on their delivery system, longer lasting.

Opioids have numerous effects on the central nervous system, including analgesia (pain relief), euphoria, depression of the nervous and respiratory systems, cough suppression, and

constipation. With respect to analgesia, unlike other non-opioid analgesic drugs, opioids can reduce both the sensory and affective (emotional) components of pain. Opioids relieve severe, constant pain from tissue injury, such as after trauma or a surgery but appear to be largely ineffective for intermittent shooting pain caused by nerve damage. Opioids can do a good job controlling pain when someone is not moving but a poor job blocking movement–triggered pain.

19. Many patients experience euphoria or a pleasant floating sensation with lessened anxiety and stress especially when taking an opioid for the first time. In general, the greater an opioid's potency and the faster it crosses into and acts on the central nervous system, the more likely the person will experience euphoria and a floating sensation. In the case of oxycodone, there has been growing concern that oxycodone is not merely a compound with superior bioavailability (better oral absorption than morphine), but possessed other properties that increased its abuse liability (Remillard, Kaye, and McAnally 2019). These include that unbound oxycodone concentrations in brain at steady state will be approximately six-fold higher than those of morphine due to differences in the extent of blood-brain barrier transport (oxycodone > morphine) (Bostrom, Hammarlund-Udenaes, and Simonsson 2008). In addition, the action of oxycodone has been shown to have an enhanced ability to evoke the stable increase in dopamine concentrations as well as the phasic properties of dopamine release in a critical reward site of the brain, the nucleus accumbens (Vander Weele et al. 2014). Taken together, these reports suggest that oxycodone represents an opioid analgesic with increased abuse potential.

20. Opioids act on the nervous system in many ways, but they generally act as nervous system depressants causing sedation—drowsiness and clouding of mentation. Opioids that have full activity (affinity – efficacy) at the mu opioid receptor, will dose-dependently

decrease the breathing rate. Independent of their role in treating pain, weaker opioids are routinely used for cough suppression.

21. Some of the most medically concerning effects of opioid use in the context of chronic use are tolerance, dependence, and addiction. Tolerance refers to the problem of repeated doses of opioids having a diminishing analgesic effect. Chronic opioid users will also develop a tolerance to the other opioid effects such as respiratory depression, although this does not protect them from fatal overdose. Opioid tolerance develops at different rates to different effects. The exception to opioid tolerance is constipation; the body does not develop a tolerance to this effect. With respect to pain relief, after repeated doses, attaining the same quality of analgesia experienced with early exposure to opioids requires progressively increasing the dose and or potency of the opioid. Despite dose increases, it is rare that a patient will have the same degree of analgesia experienced during their initial dose.

22. Physical dependence accompanies tolerance to repeated administration of opioids. For example, after a period of regular opioid administration, failure to continue the drug results in withdrawal or an abstinence syndrome (an exaggerated rebound of the nervous system from having lost its suppressed state). In the context of long-term use, dependence is not only physical, but psychological, and becomes much harder to reverse.

23. Addiction is a primary, chronic disease of brain reward, motivation, memory, and associated circuitry. Dysfunction in these circuits leads to characteristic biologic, psychological, and social manifestations. Addiction is characterized by inability to abstain consistently, impairment in behavioral control, cravings, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. A

pneumonic is the four C's: Cravings, loss of Control of amount or frequency of use, Compulsion to use, use despite Consequences.

2. What is pain?

a. Pain is a perception.

24. The International Association for the Study of Pain (IASP) defines "pain" as "unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." Pain is always subjective, even when it is associated with objectively observable tissue damage.

b. Chronic pain is not simply another day of acute pain.

25. Chronic pain is frequently defined as pain that lasts beyond the normal tissue healing time, and generally estimated at pain lasting 3 months or longer.

26. Chronic pain encompasses a complex condition that has defied simple remedies. Persistent pain has been classified as chronic if someone has endured it for at least three months. Unfortunately, over this time period, the person experiencing chronic pain may have changed in complex ways. A single therapeutic switch to turn off the perception of chronic pain has yet to be found and in fact may not exist. From the neuroscientist's perspective, pathologic plasticity changes in the central and peripheral nervous system have taken hold and have become self-perpetuating, signaling pain and frequently limiting meaningful function. It often is associated with negative changes in mood, driving depression and social isolation. From the perspective of those suffering chronic pain, any remedy, even one that may simply remit the pain for a few hours or days, may be a welcome relief despite risks or side effects. Importantly, just as chronic pain represents a complex pathophysiologic condition that develops over time, the successful management of chronic pain often requires an equally complex and time-intensive approach to

diminish or resolve. While opioids can provide effective immediate pain relief, they do not reverse the pathophysiologic states of chronic pain.

3. History of Opioid Use

27. Over the past 25 years the United States has experienced an unprecedented increase in opioid-use disorder (OUD, which is sometimes used interchangeably with "addiction"), opioid overdose, and other opioid-related harms. As of 2017, 2.1 million Americans aged 12 years or older had an OUD involving prescription opioids, and about 700,000 had an OUD involving heroin, an illicit opioid (HHS 2018). Drug overdose, driven primarily by opioids, is now the leading cause of unintentional injury death in the United States. Two out of three drug overdose deaths involve an opioid (Hedegaard H 2018). Overdose deaths from opioids have increased almost six times since 1999 (CDC 2018). Overdoses involving opioids killed more than 47,000 people in 2017, and 36% of those deaths involved prescription opioids (Scholl et al. 2018). This increase in opioid-related deaths has occurred in tandem with an equally unprecedented increase in the prescribing of opioid medications for purposes of pain management.

28. This latest chapter in the modern medical use of opioids in this country represents a significant departure from the one preceding it. Below I provide a brief outline of the historical context leading up to the current situation.

a. For centuries, doctors have known that opioids are one of the most potent analgesic agents available, but they have also known that opioids are highly addictive.

29. Opioids have been used for medicinal and recreational purposes for millennia. While the use of opioids for treatment of acute severe pain has generally been accepted, their use for managing chronic noncancer pain has been controversial since the 19th century, with the popular view shifting over the decades between broad acceptance versus a more restrictive

perspective (Courtwright 2001). The tension between the desire to make opioids available to those who may benefit from them and the recognition that opioids are addictive drugs with societal consequences was heightened with medical developments that occurred during the 1800s (Musto 1999; Booth 1996; Courtwright 2001). These developments included the extraction of morphine from opium in 1803 and the development of the hypodermic needle (which can be used to inject morphine to relieve pain) in the 1850s (Courtwright 2001). Morphine was used widely for pain management during the American Civil War, and many soldiers developed opioid addiction or "morphinism." With few effective alternatives, moreover, many medical professionals used morphine to treat chronic pain conditions. This and the nonmedical use of opioids were major drivers of an opioid addiction epidemic that took place in the latter 19th Century (Courtwright 2015).

30. By the late 1800s, scientists were starting to recognize the problem of opioid addiction, and a policy response began to emerge. What is thought to be the first accurate and comprehensive description of addiction to morphine was produced in 1877. In hopes of developing a less addictive alternative to morphine, heroin (diacetylmorphine) was synthesized in 1874 (although it was later found to be more potent than morphine). Medical professionals became increasingly critical of the use of opioids to treat pain and lobbied successfully for state and local laws to control the sale of opioids and other narcotics. Consumption of medicinal opioids declined as a result (Courtwright 2015).

31. Reform efforts continued in the early 20th century. The Harrison Narcotics Act, enacted by Congress in 1914, required persons who imported, produced, sold, or dispensed opium-based drugs (as well as coca-based drugs) to register, pay a tax, and keep detailed records that officials could use in enforcing laws to restrict opioid transactions to legitimate medical

channels. This act had the effect of criminalizing the use of opium for nonmedical purposes (Courtwright 2015; Hoffman 2016). The use of heroin for medicinal and other purposes was specifically banned by the Heroin Act, enacted in 1924.

32. The consensus among medical professionals for most of the 20th century was that opioids should not be used for the management of chronic pain because of the lack of evidence regarding their effectiveness for this type of pain and the risk of addiction. For example, in a survey of physicians in the early 1970s, "when asked why they would not go higher [in dosing meperidine] if pain persisted, 40% of the doctors stated that higher doses were no more effective, with 60% stated that higher dosages contained the danger of serious side effects." (Marks and Sachar 1973) Some researchers even concluded that doctors were under-prescribing opioids due to an exaggerated fear of addiction (Morgan 1985). Research aimed at developing new and potentially less-addictive opioids continued. Nevertheless, Percocet (oxycodone) and Vicodin (hydrocodone) which combined semisynthetic opioids with acetaminophen, became available in the 1970s for relief of moderate to moderately severe pain. These and most other prescription opioids are now regulated under the Controlled Substances Act (CSA) of 1970 as Schedule II drugs—those with a "high potential for abuse which may lead to severe psychological or physical dependence" (DEA 2019).[2]

b. Increased opioid prescribing in 1990s for cancer and palliative care

33. The stigma associated with opioids meant that they often were not used or were used sparingly even for people with terminal cancer. American physicians worked to change this approach and expand the use of opioids for cancer and palliative care.

[2] Some opioids are not classified in Schedule II. These include opioids containing less than 90 milligrams of codeine per dosage unit (e.g., Tylenol with Codeine®) and buprenorphine (used in the treatment of OUD), which are Schedule III drugs—those with "a potential for abuse less than substances in Schedules I or II" and whose "abuse may lead to moderate or low physical dependence or high psychological dependence" (DEA, 2019).

34. Globally, 8.2 million people die of advanced cancer each year. Cancer pain prevalence rises with disease progression and affects about 64% of patients with advanced cancer, and about 45% of all patients with advanced cancer experience pain of moderate to severe intensity (Patijn et al. 2007). Morphine and other strong opioids have been critical to help manage pain in advanced cancer. Historically, modern day efforts to improve pain control for patients with cancer have their roots in the mid- sixties when the first hospice was founded in England, often using opiates for treatment of end-of-life pain. However, concerns were raised in the 70s, 80s and beyond that a portion of cancer pain remained undertreated. For example, based on structured interviews, authors suggested that misconceptions about opioids probably led to undertreatment with narcotic analgesics, causing much needless suffering in medical inpatients. Upon closer examination of a case study however, the vast majority of the cases noted were pain complaints from cardiac ischemia with a single traumatic case of pain (rib fracture) and no control group or randomization (Marks and Sachar 1973). Other arguments were promoted about the undertreatment of pain (Deandrea et al. 2008; Greco et al. 2014). This included a movement in the 1980s from some cancer patients and physicians to legalize heroin for cancer pain. Given the limited study design, the relative efficacy of heroin versus morphine in the relief of chronic cancer pain remains incompletely studied (Levine, Sackett, and Bush 1986).

35. Although pain management in cancer patients differs, these variations were not explained by cancer type, duration of disease, or socioeconomic deprivation. In response to the reported disparities and undertreatment of cancer pain, there emerged initiatives to expand the scope of cancer pain care including the use of opioid analgesics (Portenoy et al. 1986; Foley 1985). The failure to use more opioids in the treatment of cancer pain was depicted as an

irrational, undocumented fear that appropriate use will lead patients to become addicted (Morgan 1985).

36. In 1986, the World Health Organization (WHO) published a "ladder" guideline for opioid use with progressive cancer pain. Even then, however, the WHO explicitly distinguished its recommendations for cancer pain from chronic pain:

> It is important to stress that a clear distinction exists between patients with chronic non-malignant pain and patients with pain from progressive cancer. Extensive clinical experience has demonstrated that, while most cancer pain responds readily to established clinical treatments, this is not true of many nonmalignant, chronic pain syndromes. Severe cancer pain commonly responds to strong opioid drugs, whereas this is not the case for most forms of non-malignant chronic pain.

('Cancer pain relief, World Health Organization' 1986). Other efforts to measure the quality and quantity of cancer pain management by measuring the amount of morphine consumed in a particular country argued against the association between increases in morphine consumption and opioid addiction. However, the data actually showed that 9 of 11 European countries with an increase in morphine consumption had an increase in overdose rates from 1986-1990 (Zenz and Willweber-Strumpf 1993).

37. Subsequently, it was emphasized that effective treatment of cancer pain often required much more than increasing doses or potencies of opioids. To better address this challenge, guidelines were developed through the "National Comprehensive Cancer Network. Adult Cancer Pain" that included recommendations to reevaluate pain at each patient visit and as needed to meet patient-specific goals for comfort, function, and safety through comprehensive pain management. This includes the consideration of a pain management specialty consultation (Comprehensive and Network 2016). Thus, even when treating pain from active cancer, best practices for pain management require a comprehensive response rather than opioids alone.

c. The multidisciplinary treatment of chronic pain provided a safe and effective model of care. But under pressure from market forces, the number of multidisciplinary pain centers declined in the 1980s and chronic pain treatment shifted back to primary care.

38. As is often noted, the scientific discipline of pain research and the medical subspecialty of pain management are relatively new fields, notwithstanding the prevalence and universality of pain (Tompkins, Hobelmann, and Compton 2017). John J. Bonica, an anesthesiologist, is widely considered to be the father of modern pain management. He designed and operated the first "multidisciplinary" pain clinic at the University of Washington in Seattle in the 1960s (Tompkins, Hobelmann, and Compton 2017). The clinic brought together clinicians from a variety of fields, including physicians, psychologists, nurses, occupational therapists, physical therapists, and vocational counselors all of whom were trained in pain management. This team would meet collectively to discuss ongoing patient care issues, and the assessment and treatment options they designed were comprehensive, including "behavioral treatment for chronic pain, physical therapy, occupational therapy, and ability to refer to specialists not offered by the team" (Tompkins, Hobelmann, and Compton 2017). This approach achieved success. The following passage from a recent paper sums up the evidence supporting multidisciplinary pain treatment:

> Due to improvement in overall patient functioning, reductions in health care expenditures and an increase in rate of patients returned to employment, the multidisciplinary pain clinic was deemed a success (Flor, Fydrich, and Turk 1992) (Kamper et al. 2015). In these published meta-analyses, multidisciplinary pain clinics were compared to single discipline treatment (e.g., physical therapy, medication management), usual medical care, and/or no treatment. Impressively, treatment gains remained evident for up to 13 years (Patrick, Altmaier, and Found 2004; Roberts, Sternbach, and Polich 1993). Analyses of patient outcomes revealed that it wasn't any single component of the clinic treatment that led to improvements in pain outcomes, but rather an effect of the concerted biopsychosocial team approach ((Linssen and Spinhoven 1992; Schatman 2010) Schatman, 2010). Subsequently, the number of pain clinics and accredited pain fellowship programs flourished, most of which used opioid therapy sparingly due to concerns of addiction and poor outcomes (Meldrum 2003). These early clinics were multidisciplinary using similar methods to Bonica's original model, or clinics focused on

> a single pain syndrome (e.g., migraine headaches) or single treatment modality (e.g., providing nerve blockade or physical therapy) (Bonica 1990).

(Tompkins, Hobelmann, and Compton 2017).

39. Yet, notwithstanding ample evidence demonstrating the effectiveness of the multidisciplinary approach (Flor, Fydrich, and Turk 1992; Turk 2002; Turk and Okifuji 1998; Guzman et al. 2001), the number of multidisciplinary pain clinics started to decline in the 1990s while the number of opioid-focused and other single modality clinics increased. This reversal has been unfortunate: multidisciplinary pain clinics that provide a form of treatment that is evidence-based and proven effective have decreased while the number of opioid-focused single modality clinics that provide a form of treatment that is nether evidence-based nor proven effective has increased. This result is even more unfortunate since one of the documented positive outcomes of the multidisciplinary approach to pain treatment was decreased use of opioids. (Turk and Okifuji 1998) (noting "[o]ne study documented that 65% of patients seen at clinics before enrolling in a pain management program used opioids compared with 20% of patients at discharge from a pain management program. Another study found that 73% of patients reduced their use of opioids while in a pain management program.").

40. The decline in the number of multidisciplinary pain clinics has been attributed to "economic" realities or factors present in the American healthcare system, primarily relating to insurance reimbursement, managed care, and the structure of academic medical facilities, which after the introduction of managed care, emphasized high profit subspecialties over multidisciplinary pain treatment programs (Tompkins, Hobelmann, and Compton 2017) (Schatman 2010). Multidisciplinary pain clinics, while providing effective and cost-efficient relief, tended not to be profit centers and were viewed by insurance companies as more expensive than other forms of pain relief. As discussed below, Purdue and other opioid

manufacturers encouraged the transition to opioid-focused treatment. But even in the absence of stand-alone multidisciplinary pain clinics, the approaches endorsed by such clinics remained safer and more effective treatment for chronic pain than opioid-focused treatment.

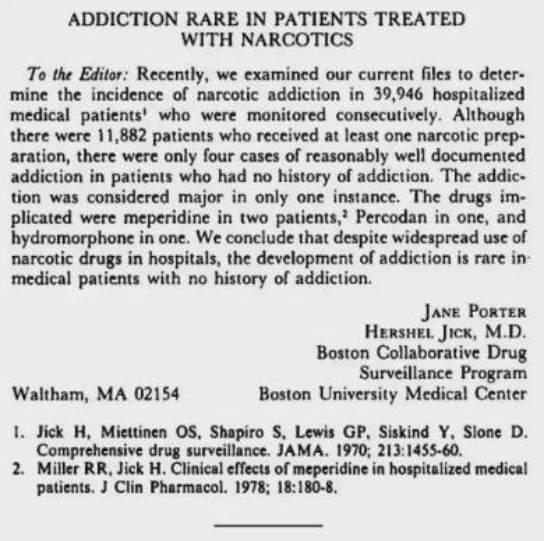
d. In the mid-nineties, OxyContin came on the scene, and there was an enormous push by Defendants to expand the use of opioids for chronic conditions, with higher doses prescribed, longer periods of treatment and for an increasing number of conditions.

41. Despite the country's history of opioid abuse and addiction during a time in which opioids were prescribed liberally for many conditions, a movement began to expand the use of opioids to provide pain relief for persons suffering from chronic pain. This movement had at its origin what appears to have been a genuine effort to replicate the success treating cancer pain in the chronic pain fields. There was debate during this early movement to expand the use of opioids for chronic pain among physicians advocating this approach, and those preferring a multidisciplinary approach to treating chronic pain that was showing significant evidence of effectiveness, as discussed above (Munglani 2019).

42. Against this backdrop, and the desire of the medical community to provide effective pain relief for the many Americans suffering from chronic pain, came a new opioid formulation that promised relief without the risk of addiction and abuse that so marked the history of opioids. In 1995 the FDA approved OxyContin (oxycodone controlled-release), which was manufactured by Purdue Pharma and marketed as allowing dosing every 12 instead of every 4 to 6 hours (FDA, 2017c). Purdue marketed OxyContin aggressively to providers and patients in the years following its release to the market in 1996 (Meldrum 2016). This marketing drove the prescription of OxyContin / oxycodone at higher doses, longer periods of treatment, and for an increasing number of conditions—despite evidence of high abuse potential.

43. Purdue and other manufacturers took the message of expanding opioid use that the cancer and palliative care specialists had begun to advance and amplified it. By repeatedly citing two pieces of "evidence" and sponsoring multiple presentations on the topic, the manufacturers multiplied the reach of this message by many times more what it otherwise would have been for an academic research physician publishing papers. This was despite the fact that one of the two sources repeatedly cited was only a letter to the editor and had a very limited scope given it reviewed files of hospitalized patients who had received "at least one narcotic preparation" while in the hospital to determine the incidence of addiction (Porter and Jick 1980):

.



ADDICTION RARE IN PATIENTS TREATED WITH NARCOTICS

To the Editor: Recently, we examined our current files to determine the incidence of narcotic addiction in 39,946 hospitalized medical patients[1] who were monitored consecutively. Although there were 11,882 patients who received at least one narcotic preparation, there were only four cases of reasonably well documented addiction in patients who had no history of addiction. The addiction was considered major in only one instance. The drugs implicated were meperidine in two patients,[2] Percodan in one, and hydromorphone in one. We conclude that despite widespread use of narcotic drugs in hospitals, the development of addiction is rare in medical patients with no history of addiction.

JANE PORTER
HERSHEL JICK, M.D.
Boston Collaborative Drug Surveillance Program
Waltham, MA 02154 Boston University Medical Center

1. Jick H, Miettinen OS, Shapiro S, Lewis GP, Siskind Y, Slone D. Comprehensive drug surveillance. JAMA. 1970; 213:1455-60.
2. Miller RR, Jick H. Clinical effects of meperidine in hospitalized medical patients. J Clin Pharmacol. 1978; 18:180-8.

44. Manufacturers nonetheless cited this letter for the broad claim that fewer than 1% of patients treated with opioids would develop addiction, as discussed below.

45. As later reviewed by Leung et al, this single letter to the editor, leveraged by Purdue in support of OxyContin, was subsequently cited 608 times, while other letters to the editor published contemporaneously were cited a median of 11 times (Leung et al. 2017). Although the Porter & Jick letter was published in 1980, it was cited most frequently between

1996 and 2002, with the highest frequency in 1996, the same year that Purdue began marketing OxyContin (Leung et al. 2017).

46. Nor did the other source most frequently cited provide strong evidence supporting chronic opioid use (Portenoy and Foley 1986). Portenoy and Foley sought to demonstrate that opioid maintenance therapy can be a safe, salutary and more humane alternative to the options of surgery or no treatment in those patients with intractable non-malignant pain and no history of drug abuse. However, these conclusions were built on a very limited case study that was descriptive rather than analytic, with small non-random patient selection and where two-thirds required less than 20 morphine equivalent mg/day (Portenoy and Foley 1986). At best, this study supported a conclusion that more study was needed. It did not support the conclusions that Purdue and other opioid manufacturers claimed to expand the market for prescription opioids.

47. Although there was little dispute at the time of the importance of more effectively treating cancer pain, an overwhelming emphasis on opioids appeared to take hold with the expanded use of OxyContin over more comprehensive approaches to treat pain. Purdue used the oncology market as an entrée for OxyContin, but its sales representatives then quickly moved to primary care, with the message to treat not only cancer pain but essentially all moderate to severe painful conditions with OxyContin/oxycodone, as discussed in more detail below.

48. Purdue essentially co-opted the messaging coming out of the cancer pain movement and advanced the notion that opioids were an ideal therapeutic solution, underused for the long-term management of chronic pain, and that the risks of addiction were very small. Purdue recognized, however, that if OxyContin was considered a cancer drug, doctors would be reluctant to use it more broadly. To avoid this result, Purdue scrupulously avoided comparing

OxyContin to the opioid most associated with cancer (morphine) or stating that OxyContin was a strong as morphine (when in fact the oxycodone is stronger).

49. In 1996, the American Academy of Pain Medicine and American Pain Society issued a joint consensus statement titled *The Use of Opioids for the Treatment of Chronic Pain*, describing potential benefits of using opioids for management of chronic pain (including non-cancer) (Haddox et al. 1997). This included statements that promoted the use of opioids for chronic non-cancer pain, that the risk of prescription opioids causing addiction was a myth, and chronic pain can be measured on a 0 to 10 scale as easily as acute pain (Campbell 1996). Moreover, it was argued by this group that studies indicate that the de novo development of addiction when opioids are used for the relief of pain is low and the risk of opioid-induced respiratory depression tends to be a short-lived phenomenon that generally occurs only in the opioid-naive patient, and is antagonized by pain (Haddox et al. 1997)—a dangerous position that was never grounded in rigorous science and has been proven wrong (Dowell, Haegerich, and Chou 2016).

50. There were also concerted efforts by pain specialists funded significantly by Purdue and the other opioid manufacturers to persuade state medical boards and state legislatures to remove legal impediments to opioid-based pain treatment (Hoffman 2016). This was accompanied by a campaign to call public and professional attention to the prevalence of pain and its seriousness as a public health problem. This concept was also supported by the American Academy of Pain Medicine and American Pain Society to advocate for the interests of pain patients suggesting that pain be considered a "5th vital sign," ostensibly in an effort to improve pain assessment and treatment. (Campbell 1996). Although increasing attention was drawn to the assessment and treatment of pain, there was little to no progress in the development of novel pain

therapies. The intersection of a greater societal focus on pain management and pain as an emerging 5th vital sign, without any fundamental advance in analgesics beyond more opioids, left physicians searching for solutions—a marketing opportunity capitalized upon by pharmaceutical companies emphasizing the effectiveness and safety of new extended-release opioids.

51. With the incorporation of measuring pain as the 5th vital sign, it soon became apparent that its application was not providing its intended outcome—the improvement of pain care. In a retrospective study of 300 visits before and after the institution of the 5th vital sign, Mularski and colleagues found no improvement in pain management (Mularski et al. 2006). More concerning was that, following the institution of the 5th vital sign and adoption by the Joint Commission, risk to patients increased as a result. Subsequently, new standards recommend that pain assessment include identification of psychosocial risk factors that may affect self-report of pain, promote access to nonpharmacologic pain treatment modalities, and avoid 5th vital sign algorithms that would result in opioid-based patient harm (Baker 2017).

52. In the context of Purdue's substantial promotional expenditures and these changing professional attitudes, OxyContin sales rose from $48 million in 1996 to more than $1 billion by 2000 (Van Zee 2009). Sales of prescription opioids are estimated to have quadrupled between 1999 and 2010 ('Vital signs: overdoses of prescription opioid pain relievers - United States, 1999-2008' 2011), driven in part by OxyContin during the early portion of this period (GAO 2003). However, problems began to emerge by at least 2000, with reports of widespread diversion, tampering, and misuse of OxyContin (Cicero, Inciardi, and Munoz 2005) (GAO 2003; Hoffman 2016). In response, the FDA changed the OxyContin label in 2001 "to add and strengthen warnings about the drug's potential for abuse and misuse" and in 2003 issued a

warning letter to the manufacturer regarding promotional materials that omitted and minimized the drug's safety risks (FDA 2017).

53. Nonetheless, sales of prescription opioids continued to increase (Pan 2016). The increase in opioid prescribing that began during the 1990s was associated with a parallel increase in opioid-related substance use disorders and opioid-related deaths (Dowell, Haegerich, and Chou 2016; Kolodny et al. 2015). Using conservative estimates excluding non-methadone synthetics, prescription opioids overdoses accounted for 17,087 deaths in 2016, up from approximately 3,442 in 1999 (Seth et al. 2018). While there are indications that opioid prescribing is decreasing, as recently as 2017, tens of millions of opioids were dispensed in the U.S. (191 million total opioid prescriptions) (CDC 2017). Although recent data do show a leveling off in opioid prescribing, rates in the United States remain at historically high levels and substantially greater than the rates seen in other industrialized Western countries. These high prescribing rates continue despite the lack of evidence supporting such practices and the abundant evidence of the risks and harms of opioid use. The rates of prescription and illicit opioid misuse, a shift from prescription opioids to illicit markets, overdose, and admissions to drug treatment programs have all increased in parallel to burgeoning opioid prescribing (Rudd et al. 2016).

IV. DETAILED STATEMENT OF OPINIONS

54. This opioid crisis lies at the intersection of two substantial public health challenges: containing the rising toll of opioid-related harms and reducing the burden of suffering for the tens of millions of people suffering from pain. Finding the ideal balance is a challenge for all physicians and health care providers. While there are a number of reasons why the epidemic was able to take root in the Country—from the lack of medical education on the

treatment of pain, to the market forces that caused a decrease in the availability of multidisciplinary pain treatment—there is no real question that the epidemic has been driven by an unwarranted increase in prescription opioids orchestrated by the pharmaceutical industry. The total opioid prescribing rate more than doubled in the U.S. from 1995 to 2013 (IMS Health 1997-2013). This trend is confirmed by prescription data from 1995-2010 derived from the National Ambulatory Medical Care Survey showing a substantial increase in opioid prescriptions between 1995 and 2010 in office-based medical visits, especially in visits by middle-aged and older adults and by patients making their first visit to the treating physician (Olfson et al. 2013).

A. The medical standard of care for treating both chronic and acute pain was changed because of widespread promotion and marketing of opioids that trivialized the risk of addiction and exaggerated the benefits of long-term opioid use.

55. As part of our work on the NASEM Consensus Study Report, my colleagues and I relied on a traditional multi-factorial causal model commonly used in public health, ranging from structural factors to individual susceptibility. Using this approach, we found certain hypotheses about "causes" of the epidemic to be inescapable. Of particular note, data present a prima facie case that heavy promotion of opioid prescribing by Defendants (including misleading claims), substantially increased prescribing by physicians and was the key contributor to the increase in misuse, OUD, and accompanying harms. (Van Zee 2009; GAO 2003; Hoffman 2016; Cicero, Inciardi, and Munoz 2005; 'Vital signs: overdoses of prescription opioid pain relievers - United States, 1999-2008' 2011).

56. Opioid manufacturers took advantage of physicians' desire to provide relief to large population of people with chronic pain conditions. In 2016, the CDC estimated 50 million US adults suffer chronic pain, defined as reporting pain every day or most days over the past 6 months; and 19.6 million U.S. adults suffer from "high-impact chronic pain," defined as chronic pain that frequently limits life or work activities (Dahlhamer et al. 2018). The CDC explains:

"National estimates of high-impact chronic pain can help differentiate persons with limitations in major life domains, including work, social, recreational, and self-care activities from those who maintain normal life activities despite chronic pain, providing a better understanding of the population in need of pain services." (Dahlhamer et al. 2018) Chronic pain, however, is complex and difficult to treat.

57. While multidisciplinary pain treatment demonstrates substantial effectiveness, for the reasons discussed above, access to this type of treatment diminished in the 1990s. Yet, of course, physicians' desire to help their patients remained. It is, thus, particularly unfortunate from a public health perspective that it was at this precise moment that Purdue's unprecedented marketing campaign for OxyContin took shape (GAO 2003). It was fertile ground for a campaign based on the promise that these opioids were new and improved and specifically designed to provide effective relief for chronic pain with very low risk of addiction.

1. The campaign to persuade doctors to prescribe "new" opioids

58. In my opinion, the driving force of this national catastrophe has been the introduction and marketing of long-acting formulations of high potency opioids such as OxyContin beginning in 1996. Physicians were misled through Defendants' marketing and sales detailing intended to persuade doctors to accept that more potent and long-acting formulations of opioids (such as OxyContin) were safe and effective in the treatment of multiple forms of pain, especially chronic non-cancer pain, and even at high doses.

59. Purdue and other Defendants utilized a number of approaches to encourage physicians to prescribe opioids broadly for the treatment of chronic pain. They engaged in direct-to-consumer marketing. They marketed directly to physicians through sales representatives. They funded research, pain-related medical societies, and continuing medical education, lobbied medical boards and agencies responsible for pain-related treatment guidelines,

and lobbied state and local government to remove barriers to broader use of opioids for the treatment of pain. ('Fueling an epidemic. Exposing the financial ties between opioid manufacturers and third party advocacy groups' 2018). A common feature across all of these efforts to promote the broader use of opioids was the message that the risk of addiction was rare, and the benefits of long-term opioid use were well established. These efforts were remarkably successful:

> An in-depth analysis of the promotion and marketing of OxyContin (Purdue Pharma, Stamford, CT), a sustained-release oxycodone preparation, illustrates some of the key issues. … OxyContin's commercial success did not depend on the merits of the drug compared with other available opioid preparations. The *Medical Letter on Drugs and Therapeutics* concluded in 2001 that oxycodone offered no advantage over appropriate doses of other potent opioids. Randomized double-blind studies comparing OxyContin given every 12 hours with immediate-release oxycodone given 4 times daily showed comparable efficacy and safety for use with chronic back pain and cancer-related pain. … In 2001 alone, the company spent $200 million in an array of approaches to market and promote OxyContin.
>
> From 1996 to 2001, Purdue conducted more than 40 national pain-management and speaker-training conferences… Purdue promoted among primary care physicians a more liberal use of opioids, particularly sustained-release opioids. …
>
> Purdue's promotion of OxyContin for the treatment of non–cancer-related pain contributed to a nearly tenfold increase in OxyContin prescriptions for this type of pain, from about 670 000 in 1997 to about 6.2 million in 2002… Prospective, randomized, controlled trials lasting at least 4 weeks that evaluated the use of opioids for chronic, non–cancer-related pain showed no consistent improvement in physical functioning. …
>
> When OxyContin entered the market in 1996, the FDA approved its original label, which stated that iatrogenic addiction was "very rare" if opioids were legitimately used in the management of pain. In July 2001, to reflect the available scientific evidence, the label was modified to state that data were not available for establishing the true incidence of addiction in chronic-pain patients [and] also deleted the original statement that the delayed absorption of OxyContin was believed to reduce the abuse liability of the drug.
>
> …Purdue funded more than 20 000 pain-related educational programs through direct sponsorship or financial grants, providing a venue that had enormous influence on physicians' prescribing throughout the country.

(Van Zee 2009). Evidence I have reviewed, including Defendants' internal communications, sales representative training materials and call notes, and promotional materials supports Dr. Van Zee's conclusions. A number of examples of this information are attached to my report as Exhibits A-C. These examples are not intended to be exhaustive, but, rather, illustrative of the Defendants' actions.

60. It is my opinion that as a result of direct-to-consumer and direct-to-physician marketing, as well as other efforts by opioid manufacturers to promote the widespread and long-term use of opioids, that the risk of addiction was trivialized, and the benefits of long-term opioid use overstated. Physicians were influenced by these efforts and a cautious and conservative approach to the use of opioids for the treatment of pain was replaced with much more liberal prescribing practices. I observed this firsthand in my own training after emerging from residency in 1995 to find increasing use of more potent formulations of opioids and sustained-release opioids for acute and chronic noncancer pain.

2. Specific misstatements designed to encourage physicians to overcome their reluctance to prescribe opioids liberally for chronic pain

61. Opioid manufacturers promoted chronic use of opioids based upon a set of key misrepresentations. These included the following: (1) taking long-acting opioids as prescribed for pain protects against addiction and abuse; (2) that new opioid formulations had no ceiling dose and were safe at high doses; and that (3) chronic opioid therapy improves function and quality of life. These misrepresentations appeared in print promotional materials and were also repeated by sales representatives in their direct marketing to physicians. In addition, (4) Purdue, at OxyContin's launch, took advantage of and was careful to maintain the perception that oxycodone is less potent than morphine, when in fact it is more potent.

a. Opioid manufacturers claimed taking long-acting opioids as prescribed for pain protects against addiction and abuse.

62. As discussed above, in 1996 when OxyContin was released, physicians generally were reluctant to prescribe opioids on a long-term basis because of fears of addiction. Purdue, of course, knew this through market studies that demonstrated this concern. Purdue admitted this when it pled guilty in 2007 to misbranding OxyContin:

> During the period February through March l995, PURDUE supervisors and employees obtained market research that included focus groups of forty primary care physicians, rheumatologists, and surgeons to determine their receptivity to using OxyContin for non-cancer pain. According to this market research, some of these physicians had concerns, similar to their concerns about combination opioids, regarding OxyContin's addictive potential and side effect profile, including that "[t]he biggest negative of [OxyContin] was the abuse potential."

See Agreed Statement of Facts, *United States. v. Purdue Frederick Co.*, No. 1:07-cr-00029 (W.D. Va. May 10, 2007) ("Purdue Guilty Plea") at §19. Internal documents produced in discovery confirm Purdue's knowledge of physicians' reluctance to prescribe opioids for non-cancer pain. *See* Exhibit C. For example, notes from a June 9-11, 1995 OxyContin Investigators' Meeting indicate that "among health care providers there is a perception that patients feel a 'stigma' associated with opioid analgesic therapy. Morphine and hydromorphone are most associated with this stigma. One of the patients' biggest fears appears to be the possibility of addiction…" PKY181823986 at 17 (*See* Exhibit C-2).

63. Sales representatives used multiple approaches to persuade physicians who expressed caution and concerns about the abuse and addiction potential of oxycodone and OxyContin. *See* Exhibit A. This amounted to repeated falsehoods that OxyContin / oxycodone had a decreased potential for addiction, was superior to and a less addictive alternate than combination forms of opioid analgesics containing hydrocodone (equal potency to morphine)

and acetaminophen. One of the ways Purdue overcame this reluctance was by persuading doctors that OxyContin was a "new" formulation of oxycodone that was less likely to be abused or lead to addiction. *See* Exhibit A-1.1, Exhibit B-1-15. OxyContin is simply oxycodone (which was developed in 1917) in a timed-release formulation that Purdue argued allowed a single dose to last 12 hours, mitigating the potential for addiction. Specifically, Purdue said, the extended-release mechanism maintained drug levels at constant levels. *See* Exhibit A-3.1-3.6. This marketing explanation for why this pill could be used with little risk of addiction, while plausible (because highs and lows (or "peaks and troughs") were understood to be tied to the development of addiction) lacked scientific proof. At no point was this marketing claim—or the use of opioids for chronic pain generally—supported by reliable evidence of the type that should have accompanied widespread marketing of the drug. Indeed, Purdue eventually admitted that its statements claiming that its extended release formulation made OxyContin less addictive than immediate release formulations was false and misleading (*see* Purdue Guilty Plea).

64. Moreover, Purdue knew from its own pharmacokinetic studies that OxyContin's peaks and troughs were not significantly different from those of IR oxycodone, but Purdue concealed that data. Purdue admitted this deception in the Purdue Guilty Plea at §§21-27. In fact, for many patients, OxyContin only lasted for 8-hours, after which patients would experience a decline in analgesic effect (or trough). Purdue worked to prevent physicians from prescribing OxyContin Q8 (or every 8 hours) despite its knowledge that this end-of-dose drop-off was common. *See* Exhibit A-3For example, an exhibit that refers to "Q12h vs. Q8h Warfare," indicates that sales representatives were told, "the action of adding a dose, as opposed to increasing the Q12h dose, needs to be nipped in the bud. NOW!!." They were further advised that "the war is on – OxyContin is a true 12h product. Help the MD see that 12h is appropriate

dosing for the patient controlling the pain, enhancing quality of life, even if it means using an escalating dosage and number tablets." PPLP003996830 (*See* Exhibit A-3.6).

65. It is evident from Purdue salesperson call notes that Purdue heavily marketed this purported steady state, 12/hr efficacy of OxyContin and purportedly lower abuse potential. *See* Exhibit B. For example, a September 20, 1999 call note from Ohio states:

> SAYS USES OXY, MOSTLY FOR NURSING HOME PATS. HE SAID HE HEARD IT NOW HAD A LOWER BACK PAIN INDICATION -- TOLD HIM STUDIES HAVE BEEN DONE FOR BACK PAIN, OSTEOARTHRITIS, AND CANCER -- DISCUSSED NO CEILING, 12HR EFFICACY, BLOOD LEVELS, LOWER ABUSE POTENTIAL. DISCUSSED FAST FOR NURSING HOME PATS.

Exhibit B-7, PPLPMDL0080000001 (excel spreadsheet, row 129292). Another call note from Ohio dated November 7, 1997 states:

> ALWAYS RELUCTANT TO USE NARCS BUT TOLD IF GOING TO PUT PT ON VIC/LORT OR TYL 3, WHY NOT USE THE 12 HR DOSED, WITHOUT TYLENOL AND LESS ABUSE POTENTIAL.

Exhibit B-4, PPLPMDL0080000001 (excel spreadsheet, row 76265). And another from November 19, 1997 from West Virginia states:

> CONCERNED ABOUT ADDICTION WITH OPIOIDS. DIFFERENCE BETWEEN DEPENDENCE AND ADDICTION. LESS THAN 1% OF PATIENTS BECOME ADDICTED. CAN ABRUPTLY STOP LOW DOSES OF OXYCONTIN WITHOUT WITHDRAWAL SYMPTOMS."

Exhibit B-8, SHC-000008118.

66. Promotional information given to doctors and print advertising promoted the same false messages about 12/hr dosing, low abuse potential or risk of addiction resulting from chronic opioid use. *See* Exhibit A. In addition to misleading physicians about 12/hr dosing, Purdue and the other opioid manufacturers pushed the notion more generally that the risk of addiction was rare when prescription opioids were used "as prescribed." Thus, it was not just that 12/hr dosing, round-the-clock treatment was safer and more effective, but also that addiction was unlikely to occur—indeed it would rarely occur so long as the patients taking the pills were

in pain and were following doctors' orders. Again, this shows up in promotional materials and call notes, not only from Purdue, often citing studies that purportedly proved these points. There are many examples of this in the materials I reviewed. Some particularly troubling instances include the following:

- "In fact, the rate of addiction amongst pain patients who are treated by doctors is much less than 1%." --- Transcript of "I Got My Life Back" Purdue promotional video, featuring Dr. Alan Spanos (2000) PKY180989588 at 10 (Exhibit A-1.12).

- "Fact: Fears about psychological dependence are exaggerated when treating appropriate pain patients with opioids." --- Purdue Professional Sales Aid – Myths about Opioids (2001) PURCHI-000674082 at 11 (Exhibit A-1.13).

- "Addiction risk also appears to be low when opioids are dosed properly for chronic, noncancer pain." --- Purdue Professional Sales Aid – Myths about Opioids (2001) PURCHI-000674082 at 11 (Exhibit A-1.14).

- "Pain relief is an important medical reason to take opioids as prescribed by your doctor. Addicts take opioids for other reasons, such as unbearable emotional problems. Taking opioids as prescribed for pain relief is not addiction." --- Endo brochure, Understanding Your Pain: Taking Oral Opioid Analgesics (2004) ENDO-CHI_LIT-00084049 at 3 (Exhibit A-1.16).

- Endo, *Taking a Long-Acting Opioid: What does it mean to me?* (2008) ENDO-CHI_LIT-00024520 (Exhibit A-3.14):

  What is the risk of becoming addicted to a long-acting opioid?

  Addiction is defined as compulsive drug seeking that is beyond a person's voluntary control even if it may cause harm. Most healthcare providers who treat patients with pain agree that patients treated with prolonged opioid medicines usually do not become addicted.

- Mallinckrodt, Exalgo Learning System (training for sales representatives): MNK-T1_0001161164 at 29 (*See* Exhibit A1.19-) ("While most patients chronically taking opioids for medical reasons develop tolerance and physical dependence, the risk of addiction is low.").

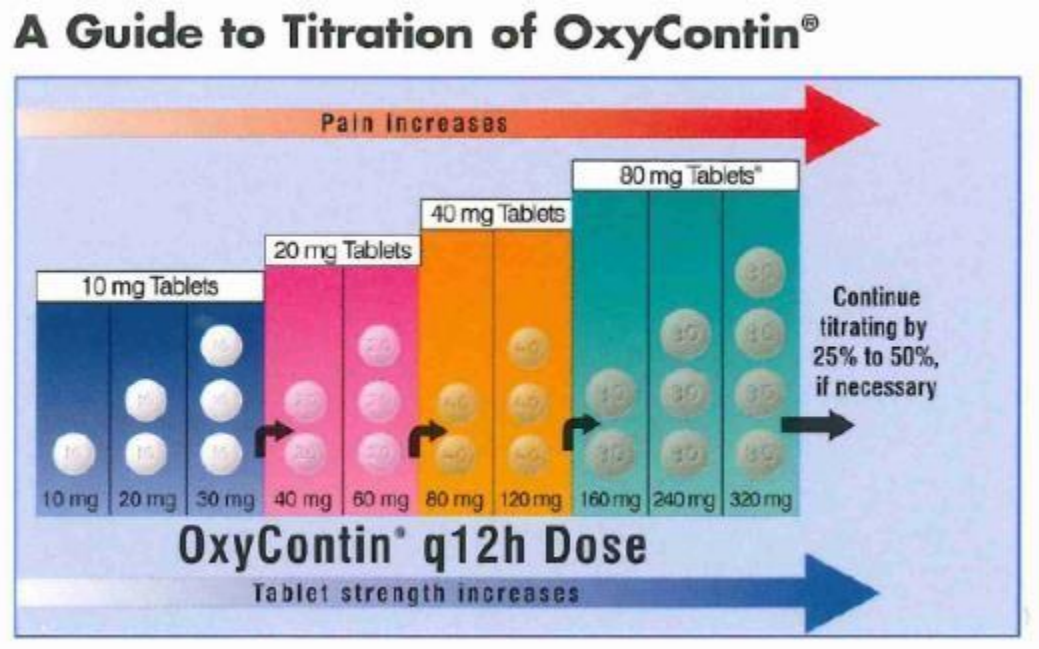
67. Overall, sales representative detailed the recurrent message that Oxycontin represented the next line in analgesic choice after NSAIDS, was superior to hydrocodone, and

had less abuse potential. Sales representatives frequently quoted the Porter and Jick letter for the claim that fewer than 1 % patients develop addiction when taking opioids for chronic pain. But there is in fact no medical evidence supporting this and other statements about the low risk of addiction, and it was misleading to suggest that the Porter and Jick letter, or the Portenoy and Foley 1986 study of 38 patients on low-dose opioids, supported these broad statements.

b. Opioid manufacturers misleadingly represented that new opioid formulations had no ceiling dose and were safe at high doses.

68. "New" ER opioids were promoted as safe at high doses unlike older low-potency combination drugs with acetaminophen. In addition, doctors were told that there were no ceiling doses for Oxycontin or other long-acting opioids.

69. There are, again, many examples of marketing and promotion materials in which doctors and patients are told that the dose can be increased safely (titrated up) until the pain is "under control." For example, a Purdue 2003 OxyContin conversion guide provided the following information, indicating no dose limit and the message to "Continue titrating by 25% to 50% if necessary":



See PDD1501128421 at 35 (Exhibit -A-3.16).

70. Similarly, a 2004 brochure from Endo Pharmaceuticals, *Understanding Your Pain: Taking Oral Opioid Analgesics* explains:

> IF I TAKE THE OPIOID NOW, WILL IT WORK LATER WHEN I REALLY NEED IT?
>
> Some patients with chronic pain worry about this, but it is not a problem.
> The dose can be increased or other medicines can be added.
> You won't 'run out' of pain relief.

ENDO-CHI_LIT-00084049 at 4 (Exhibit A-1.16).

71. Call notes also show that sales representatives pitched the notion of no dose limits and safety at high doses. *See* Ex. B. For example, a Purdue sales representative noted in a July 6, 2000 note from Ohio:

> "SPOKE WITH MD WHO EXPRESSED CONCERN RE: ONE PT RECEIVING 120 MG Q 12 FOR BACK PAIN-DISCUSSED THE PFACT THAT THERE IS NO CEILING DOSE WITH OXY LIKE SHORT ACTING; HE SEEMED TO THINK THAT THIS PT WAS ABUSING THE PRODUCT; HE NEEDS REAFFIRMATION RE: THE DECREASED ABILITY OF OXY TO BE ABUSED AND DECREASING NUMBER OF TABS…."

PPLPMDL0080000001, Exhibit B-12. Similarly, a January 19, 2001 call note from a Purdue sales representative in Ohio notes: "doc said he has been using oxy for awhile and that he uses high doses, i reminded doc there is no ceiling and that he should not worry about how high he needs to go."). PLPMDL0080000001, Exhibit B-14.

72. A particularly troubling feature of this is testimony that drug representatives received higher compensation for selling higher dose opioids.[3]

[3] *See* Exhibit A-2.1, Excerpt of Deposition of Karen White, a sales representative for Purdue from 1998 to 2002, 98:23-99:14, Dec. 17, 2003, PKY182895039("[i]t would exponentially affect our bonuses. I mean if we got the doctor, as I mentioned earlier, to write an 80 milligram instead of a 10 milligram, we would make seven and a half times more money based on what percentage of our sales that we increased over our quota."); see also Sposato Dep. 18:21-19:2, PDD9520404001. ("Q. My question is: Same amount of pills, higher dosage, Purdue makes more money for the higher dosage, correct? A. That's correct. Q. And that factors into someone's bonus, correct? A. Possibly."); ENDO-OPIOID_MDL-04908071 at 4 (2002 Endo "Tsunami Launch IC Plan" incentivized the Endo

73. The daily clinical consequences of the myth of no-ceiling dose is reflected in the increasing number of opioid-dependent patients. What was once unimaginable is now common: to see a patient taking over 500, or even 1,000 MMEs (oral morphine equivalents) daily admitted to our hospital and continue to complain of severe pain. It is a myth that there is no ceiling dose with opioids as illustrated by very real risk and consequences of overdose and death from long-term opioid therapy. Mortality rates increased gradually across the range of average daily milligrams of morphine equivalents indicating a single threshold of harm does not exist. Thus, there are no single inflection points defining a threshold of opioid risk/safety. The situation becomes even more dire if benzodiazepines are taken concurrently. The higher the dose, the higher the risk of death; this risk may occur for some patients at doses that previously were thought to be "safe." (Dasgupta et al. 2016).

74. Other studies have also examined the relationship between long-term opioids and overdose and death. Persons who received 3 or more opioid prescriptions within 90 days for chronic noncancer pain between 1997 and 2005 and received 50 to 99 mg/d of opioids (compared with 1 to 20 mg/d) had a 3.7-fold increase in overdose risk, while patients receiving 100 mg/d or more had an 8.9-fold increase in overdose risk (Dunn et al. 2010). Higher opioid doses were associated with increased risk of opioid overdose death with a maximum prescribed dose of 100 mg/d or more (Bohnert et al. 2011). When the risk of overdose was examined in patients taking a daily dose of less than 20 mg versus those with average daily doses of 200 mg or more of morphine (or equivalent), there was a nearly 3-fold increase in the risk of opioid-related mortality (Gomes et al. 2011). Other patient cohorts have shown even greater risks at a

sales force to meet the goal of "pushing higher doses" with "rewards that increased steeply" for "deeper penetration into the high-strength [Oxy/APAP] market"—defined as Percocet 7.5/325 and 10/325 and all Oxy/APAP 7.5/500 and 10/650 variants (Percocet, Endocet, and Generic Oxycodone/APAP).

threshold of intermediate dosing (>40 morphine milligram equivalents) with an odds ratio of 12.2 (CI 9.2-16.0) (Paulozzi et al. 2012).

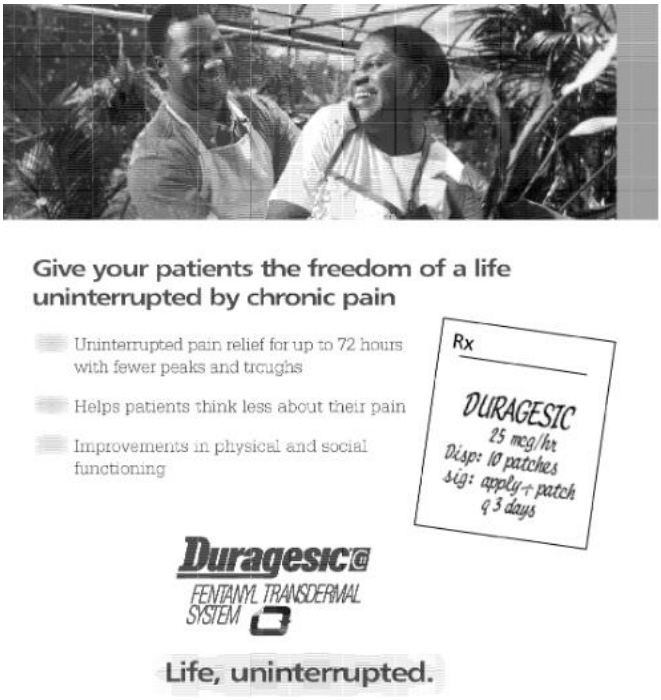
75. Taken together, with more recent studies, it appears that there is no minimum threshold below which risk of harm is zero, and risk generally increases with daily dosing. The notion that taking less than 100 MME / day is somehow safe is not supported by the literature and represents a sobering conclusion that the unnecessary initiation of long-term opioid therapy has the potential of causing great harm at any dose (Zedler et al. 2014; Bohnert et al. 2016).

c. Opioid manufacturers misleadingly represented that chronic opioid therapy improves function and quality of life.

76. Opioids were marketed for years as the panacea for pain that would give patients back their lives. The now notorious 1998 Purdue promotional video featuring Dr. Spanos, "I got my life back," painted a picture of a miracle drug at work. See PKY180989588 (Exhibit A-1.12). Patient brochures and advertisements similarly told people that opioids could improve their health, function and quality of life. Some examples include:

- "Myth: Opioids make it harder to function normally. Fact: When used correctly for appropriate conditions, opioids may make it easier for people to live normally." --- Janssen patient guide, Finding Relief: Pain Management for Older Adults (2008) JAN-MS-00476773 at 10 (Exhibit A-1.21).
- "Multiple clinical studies have shown that long-acting opioids, in particular, are effective in improving: Daily function, Psychological health, Overall health-related quality of life for people with chronic pain." --- American Pain Foundation, *A Policymaker's Guide to Understanding Pain & Its Management* at 29 (2011) (*See* Exhibit A-1.22).
- Purdue 2006 ad for OxyContin, "There can be life with relief": PDD1501614879 at 3 (Exhibit A-1.23).

- JAN-MS-00306286 at 8 (Exhibit A-1.24).



77. The impression created by these materials is that opioids are safe and effective, seldom harmful, and usually beneficial. But opioids—whether formulated as immediate-release or extended-release, and with or without "abuse-deterrent features"—are dangerous and highly

addictive. But that certainly was not the message communicated by Purdue and the other manufacturers. Instead, doctors and patients were told that studies proved that opioids would improve function and enhance quality of life for persons suffering from chronic pain. There was no scientific basis for these statements when made, and abundant evidence developed over time showing that long-term opioid therapy, rather than improving function and quality of life, leads to poor functional outcomes.

78. For example, in a Danish health study, opioid usage was significantly associated with reporting of moderate/severe or very severe pain, poor self-rated health, not being engaged in employment, higher use of the health care system, and a negative influence on quality of life. Put otherwise, opioid treatment of long-term/chronic non-cancer pain does not seem to fulfill any of the key outcome opioid treatment goals: pain relief, improved quality of life and improved functional capacity (Eriksen et al. 2006). In fact, the odds of recovery from chronic pain were almost 4 times higher among individuals not using opioids compared with individuals using opioids (Sjogren et al. 2010). There is also evidence that return to work is more often delayed than expedited for patients on chronic opioids (Von Korff 2013; Franklin et al. 2008; Franklin et al. 2009).

d. Purdue promoted and encouraged confusion about the strength of oxycodone.

79. Physicians were reluctant to prescribe opioids, particularly morphine, because of the stigma. Morphine was a cancer drug, and it was known to be highly addictive. Purdue worked around this problem by taking advantage of confusion about the active ingredient in OxyContin. Purdue knew that physicians often believed oxycodone was less powerful than morphine - when in fact, it was stronger. As explained by Purdue's former CEO Michael Friedman in an email to Richard Sackler on April 22, 1997:

> Oxycodone has a 'personality' that is influenced by many years of oxycodone use in Percocet. We have built a large part of our platform on this personality and used it to differentiate OxyContin from MS Contin and .... This differentiation has lead [sic] to much non-malignant business. Marketing is not only about what you are. It is also about what you are not. We have a success beyond our expectations that is, in part, due to the unique personality of OxyContin.

PPLP004030162 at p. 1 (Exhibit C-9). Purdue admitted that it was "well aware of the incorrect view held by many physicians that oxycodone was weaker than morphine" and "did not want to do anything 'to make physicians think that oxycodone was stronger or equal to morphine.'" Purdue Guilty Plea at ¶29. Similarly, and as noted above, Purdue was careful not to describe OxyContin in any way that suggested that it was as strong as morphine – when in fact, it was stronger. Examples of this are provided in Exhibit C, including:

- Email from M. Cullen, June 2, 1997, PPLP004032323 at p. 4 (Exhibit C-6) ("Since the non-cancer pain market is much greater than the cancer pain market, it is important that we allow this product to be positioned where it currently is in the physician's mind. If we stress the "Power of OxyContin" versus morphine, it may help us in the smaller cancer pain market, but hurt us in the larger potential non-cancer pain market. Some physicians may start positioning this product where morphine is used, and wait until pain is severe before using it…. It is important that we not change the position perception of physicians towards oxycodone when developing promotional pieces, symposia, review articles, etc..").

- Friedman Email to R. Sackler, May 28, 1997, PPLP004030150 at 1 (Exhibit C-5 at 5) ("it would be extremely dangerous, at this stage in the life of this product, to tamper with this 'personality,' to make physicians think the drug is stronger or equal to morphine.").

80. Doctors were reluctant to prescribe morphine for chronic pain because they understood the risk of abuse and addiction. By perpetuating confusion regarding the strength of oxycodone, and the purportedly less-addictive attributes of the extended-release mechanism, Purdue changed prescribing practices.

B. Opioid manufacturers took advantage of their ability to influence physicians through direct-to-physician marketing, medical education, and industry-sponsored and -funded KOLs.

81. Opioid manufacturers took advantage of physicians' desire to provide relief to the large population of people with chronic pain conditions. Chronic pain is complex and difficult to treat. While multidisciplinary pain treatment demonstrative substantial effectiveness, for the reasons discussed above, access to this type of treatment diminished in the 1990s. Yet, of course, physicians' desire to help their patients remained. It is, thus, particularly unfortunate from a public health perspective that it was at this precise moment that Purdue's unprecedented marketing campaign for OxyContin took shape. It was fertile ground for a campaign based on the promise that this opioid was new and improved and specifically designed to provide effective relief for chronic pain with very low risk of addiction.

82. Studies show that detailing is effective.[4] In addition, KOLs and mentors play a significant role educating physicians. They are highly influential, they are trusted – when a department head, or well-known and prominent academic physician says this is how you treat this condition, doctors follow suit. Residency is hierarchical; residents are students who learn from their seniors, like an apprenticeship. And when presented with studies supporting the view of the KOLs – that is influential, too.

83. Although it is unknown precisely the depth of the influence opioid-related industries such as Purdue may have had on academics, published literature and their influence on

[4] See e.g., Datta A and Dave D. Effects of Physician-directed Pharmaceutical Promotion on Prescription Behaviors: Longitudinal Evidence. Health Economics. April 2017;26(4):450-469; Stros M and Lee N. Marketing dimensions in the prescription pharmaceutical industry: a systematic literature review. J of Strategic Marketing 2015;23(4):318-336; Anon. Persuading the Prescribers: Pharmaceutical Marketing and its Influence on Physicians and Patients. November 11, 2013. http://www.pewtrusts.org/en/research-and-analysis/fact-sheets/2013/11/11/persuading-the-prescribers-pharmaceutical-industry-marketing-and-its-influence-on-physicians-and-patients Accessed August 13, 2018; Gonul, F., Carter, F., Petrova, E., & Srinivasan, K. (2001). Promotion of prescription drugs and its impact on physicians' choice behavior. Journal of Marketing, 65, 79–90.

.

faculty as Key Opinion Leaders, the failure to disclose industry-academic relationships is insidious and has undoubtedly impacted the practice of a generation of providers and trainees (Fauber 2011a). When confronted with conflict of interest, some academic centers have curtailed their relationships with these industries (Fauber 2011b).

84. These and other forces were brought to bear on providers both in private practice and academics and I believe exerted a strong influence. As a result, the standard of care was changed across the country. Compounding the problem was the limits of medical education on how to treat pain generally, and especially chronic pain. There is no common pain management curriculum that is broadly utilized for US medical, dental, pharmacy, or nursing schools that would be of similar rigor as, for example, the evaluation and treatment of chest pain. As of 2010, a survey of 117 US and Canadian medical schools concluded that pain curriculum was limited in time and scope (Mezei and Murinson 2011).

85. Although the majority of medical schools contain some pain curriculum, it is primarily embedded in other core course structures and is not generally regarded as a stand-alone topic. Alternately, much of pain management has been taught on the wards from senior to junior trainees. In 2010, the National Institutes of Health (NIH) Pain Consortium held a workshop on the state of pain education in the United States—overall there was inadequate education and training in pain management across the country. Opioid manufacturers took advantage of this education vacuum. Through the message that doctors could provide chronic pain relief to their patients, with simply the administration of OxyContin every 12 hours, and with very effective messengers—both drug representatives and prominent medical leaders in the field of pain management—the standard of care for treating pain was changed.[5]

[5] The fact that detailing is proven to be highly effective means that it has the potential to influence provider practice, and it has also been shown to be effective prescriber education outside of the sales context, with what is referred to

C. For the vast majority of chronic pain patients, the risks of prescription opioids significantly outweigh any benefits, and that at most, a small percentage of chronic pain patients achieve meaningful relief from the long-term use of opioids

86. At most, opioids are properly indicated for the short-term treatment of severe acute pain (e.g. trauma or post-surgical pain); end-of-life pain/hospice care; and cancer pain from active malignant disease. Chronic opioid therapy is not recommended for most common chronic pain conditions, including low back pain, centralized pain such as fibromyalgia, and headache pain. In less common chronic pain conditions (such as pain from advanced multiple sclerosis, sickle cell disease, pain following spinal cord injury and paraplegia, or post-herpetic neuralgia), which comprise a small percentage of chronic pain patients, opioids may be considered a third-line therapy (taken if other therapies are ineffective or contraindicated) for moderate and severe pain. However, in other neurologic conditions such as polyneuropathy, no functional status markers were improved by long-term use of opioids, adverse outcomes were more common among patients with polyneuropathy receiving long-term opioids, including depression opioid dependence and opioid overdose (Hoffman et al. 2017).

87. In addition to diagnosis, clinicians should consider risk, and some patients may not be suitable candidates on the basis of that risk.

88. Given the narrow categories that may indicate opioids for chronic use, opioids' position as third-line therapy, and the significant risks associated with its use, long-term opioid therapy for persons with chronic pain conditions is, at most, indicated in fewer than 5% of patients with chronic pain and likely significantly fewer, as explained below.

---

as "academic detailing" or sometimes "systems consultation." See Avorn J, Soumerai SB. Improving drug therapy decisions through educational outreach. A randomized controlled trial of academically based "detailing." N Engl J Med 1983; 308:1457-1463. As providers search for professional guidance in applying emerging evidence to their opioid prescribing practices, such educational detailing from trusted colleagues will be critical to separate fact from fiction among the pervasive marketing environment that surrounds the current practice of medicine in the United States.

89. For all proper indications other than terminal cancer, palliative care and hospice care, if prescribed, opioids should be prescribed with the lowest effective dose of immediate-release opioids taken only when needed.

1. Opioids are not recommended for most common chronic pain conditions.

90. The use of opioids for the management of chronic pain represents the rationale for the prescribing of a large percentage of overall opioid medication consumed each year in the United States. Common types of pain for which these drugs are prescribed include back pain, arthritis, and neuropathic pain (e.g., pain involving tissue injury). Yet there is only minimal evidence of effectiveness of opioids for successful management of chronic pain from rigorous studies lasting more than 6 weeks (Chou et al. 2015). Amongst the complications now associated with the chronic use of opioids for pain are withdrawal, dependence, tolerance, hyperalgesia, diversion, misuse, abuse, addiction, hypogonadism (specifically low testosterone in men, and amenorrhea/dysmenorrhea in women), falls, fractures, sleep-disordered breathing, increased pain after surgery, and poorer surgical outcomes, immunosuppression, and increases in feeding and growth hormone that can lead to weight gain. (Baldini, Von Korff, and Lin 2012; Chou et al. 2015).

91. In the case of the most common chronic pain conditions, including low back pain, centralized pain such as fibromyalgia, and headache pain, patients have better outcomes if opioid treatment is avoided. These conditions together comprise the vast majority of chronic pain complaints, with low back pain being the most commonly reported chronic pain condition. (Henschke, Kamper, and Maher 2015; Breivik et al. 2006; Gran 2003; Freburger et al. 2009).

92. Several meta-analyses examine the efficacy of opioids in specific pain conditions such as neuropathic (Gaskell et al. 2016; McNicol, Midbari, and Eisenberg 2013) and back pain (Abdel Shaheed et al. 2016; Chaparro et al. 2014). Additional analyses have included

publications reporting studies involving participants with mixed types of chronic pain (Chou et al. 2014; Pedersen et al. 2014). In general, these meta-analyses have suggested that any positive effects have been demonstrated only for relatively short terms, and that the size of the effects observed were small. Long term (>1yr) outcomes are largely lacking. Dropout in opioid studies for chronic pain due to side effects is common as is discontinuation of therapy in clinical settings making it difficult to estimate the benefits of these drugs. Essentially no widely-accepted guidelines suggest that opioids should be used as first-line analgesic therapy for a chronic pain condition.

93. Back pain is one of the top reasons people visit a primary care or family practice physician and also predominates in other clinical domains, such in the care of veterans. Opioid treatment for low back pain shows no advantage over non-opioid medication management but does significantly increase the person's risk of harm and death. The very few trials that compared opioids to non-steroidal anti-inflammatory drugs (NSAIDs) or antidepressants did not show any differences regarding pain and function. There are no placebo-randomized controlled trials ("RCTs") supporting the effectiveness and safety of long-term opioid therapy for treatment of chronic low back pain (Chaparro et al. 2013), and the clinical benefits of shorter-term opioid therapy appear relatively small in comparison to the many well-documented adverse effects (Deyo, Von Korff, and Duhrkoop 2015). Nevertheless, opioids continue to be used widely in the attempt to manage back pain. Additional more recent analyses also find little evidence of meaningful pain relief provided by opioids for low back pain (Abdel Shaheed et al. 2016; Qaseem et al. 2017).

94. Recently, a pragmatic, 12-month, randomized trial with masked outcome assessments was completed in Veterans Affairs primary care clinics. Pain intensity was

significantly better in the nonopioid group over 12 months. Treatment with opioids was not superior to treatment with nonopioid medications for improving pain-related function over 12 months. Adverse medication-related symptoms were significantly more common in the opioid group over 12 months. Results did not support initiation of opioid therapy for moderate to severe chronic back pain or hip or knee osteoarthritis pain (Krebs et al. 2018).

95. Opioids are also not recommended treatment for fibromyalgia and other centralized pain syndromes (Sluka and Clauw 2016; Clauw 2015). In a review of available treatments for the chronic pain of fibromyalgia, no evidence was found from clinical trials that opioids are effective for the treatment of fibromyalgia pain (Goldenberg et al. 2016). In fact, observational studies reported that patients with fibromyalgia receiving opioids had poorer outcomes than patients receiving non-opioids and current guidelines recommend against the use of opioids for the treatment of fibromyalgia pain.

96. Headache is another common painful complaint that is unresponsive to long-term opioid therapy (Saper and Lake 2008).

2. There is only weak evidence of benefit from chronic opioid therapy.

97. Opioid manufacturers made repeated claims that the routine use of opioids for the treatment of pain, especially chronic noncancer pain, is safe and effective. However, an examination of the studies purported to support this claim fail to provide sufficient evidence. As described below, a majority of the trials were not conducted for sufficient time, patients were highly selected, excluding by design subjects with risk for misuse and/or the trial design was by "enriched enrollment" (only including people known to benefit from the study drug), and the trials used opioid doses that are low to moderate.

98. For example, a trial intended to demonstrate pain relief in a chronic condition such as chronic lower back pain sponsored by Purdue was conducted for only five days, and in

addition, 19% of the study patients discontinued their medication before completion of the study (15 on codeine and five on acetaminophen plus codeine) (Hale et al. 1997).

99. In another study intended to support the claim that long-term repeated doses of opioids are effective and have low abuse potential, study patients were randomized to an open label, repeated-dose comparison of an anti-inflammatory drug and two opioid regimens in 36 patients with back pain (Jamison et al. 1998). However, patients continued to report moderate pain levels while taking opioids and had no change in their activity level. Although the study was under-powered to measure such an outcome, a statement was made that opioid therapy for chronic back pain was used "without significant risk of abuse." Curiously they noted that the study drug seemed to benefit mood as much as pain and "only one participant showed signs of abuse behavior." (Jamison et al. 1998).

100. In a randomized to double-blind treatment with placebo (n = 45) or 10 mg (n = 44) or 20 mg (n = 44) of controlled-release oxycodone every 12 hours for 14 days, one hundred six patients enrolled in an open-label trial intended to test "around-the-clock," controlled-release oxycodone therapy for osteoarthritis-related pain (Roth et al. 2000). However, patients with as little as one month of arthritis pain were enrolled representing chronic pain patients, and 70 patients (52.6%) discontinued study participation prematurely. Interference of pain on walking ability, general activity, normal work, and relations did not reach statistical significance. (Roth et al. 2000).

101. The treatment of neuropathic pain (PHN) in a double-blind placebo-controlled study (MONTAS) evaluated the efficacy and effectiveness of oral morphine administration using defined inclusion criteria over two weeks (Maier et al. 2002). However, trial subjects were highly enriched as only 49 of 997 patients screened fulfilled the inclusion criteria for MONTAS.

In addition, the study further defined short-term responders and other non-responders with mean pain intensity in all patients reduced by morphine from 7.8 to 5.2 (NNT: 2.2) and in 17 (35.4%) of responders from 7.4 to 2.9.

102. Other studies sought to demonstrate the longer-term efficacy of opioids in both neuropathic and musculoskeletal pain conditions, yet due to the high drop-out rate only 44% of 388 patients on open label treatments were still on opioids after therapy for between 7 and 24 months (Kalso et al. 2004). Another study, sponsored by Purdue suffered similar challenges with test subject drop out, and in this study, ambiguous adverse event reporting descriptions. For example, 67/227 = 29.9% % experienced a serious adverse effect with 13 possible test subjects with drug abuse behaviors, yet investigators reported 6 cases (2.6%) of possible drug misuse but no evidence of de novo addiction was observed. Importantly, seven persons died (Portenoy et al. 2007). Also, 133 subjects dropped out, so the denominator of 227 subjects, based on subjects who took at least one dose, is suspect, and the rate of drug abuse goes up as the numerator of cases stays the same while the denominator of subjects is decreased.

103. An enriched enrollment randomized withdrawal (EERW) design excludes potential participants who are nonresponders or who cannot tolerate the experimental drug before random assignment. Although EERW trial designs appear not to bias the results of efficacy, they underestimate the adverse effects (Furlan et al. 2011). Therefore studies to demonstrate opioids' efficacy in the treatment of chronic non-cancer pain for up to 3 months in such enriched trial schemes underestimate their adverse effects—a critical feature in the determination of the safety and efficacy of long-term opioids (Meske et al. 2018). Furthermore, efficacy in a 12-week study is an insufficient basis to extrapolate to long-term pain relief (Busse et al. 2018).

104. In a 2008 review of the evidence on efficacy, Ballantyne and Shin noted the inappropriateness of relying on randomized controlled trials (RCTs) as evidence for long-term opioid therapy, remarking that "one must ask if the randomized trial really is the best form of evidence for assessing opioid treatment of chronic pain given the artificiality of the trial setting, the tendency of trials to select 'ideal' patients, and the lack of generalizability to the wider population that is being treated outside trials." (Ballantyne and Shin 2008). Although RCTs are generally considered the gold standard of clinical evidence, the authors explain that "[i]n the end, RCTs tend to be useful only for showing efficacy for certain pain conditions, only for the length of the trial which tends to be short (up to 8 mo), and only in terms of the metrics of the trials." This is problematic in the context of long-term opioid therapy given that "[a]nalgesic efficacy, as demonstrated in randomized trials, does not necessarily predict effectiveness in terms of the larger real-life goal of providing helpful pain relief that is not compromised by adverse drug effects." The limitations of drawing on only short-term RCT studies has been noted by others, and included lack of effectiveness studies on long-term benefits and harms of opioids (Chou et al. 2009). It was also noted that chronic use of prescription opioids for noncancer chronic pain is much higher and growing faster in patients with mental health and SUDs than in those without these diagnoses (Edlund et al. 2010).

3. There is strong evidence that the risks of harms from opioid use increase with dose and duration of treatment.

105. Opioid manufacturers had no basis for representing that chronic opioid use was safe and effective. On the contrary, as evidence in this case shows, Defendants knew that the risks of harm were high and the evidence of benefit questionable. These companies nonetheless continued marketing, even as growing evidence of risk accumulated, and in fact compounded the

problem by casting doubt on the studies demonstrating increased risk, thereby creating more confusion and prolonging sales.

106. However, the risks associated with the use of prescription opioids are numerous and can be life-threatening. What factors have driven this? In the Washington State workers' compensation system, the total number of opioid prescriptions tripled between 1996 and 2002. However, prescriptions for the most potent opioids such as oxycodone (Schedule II), as a percentage of all scheduled opioid prescriptions (II, III, and IV), increased from 19.3% in 1996 to 37.2% in 2002. Among long-acting opioids, the average daily morphine equivalent dose increased by 50%, to 132 mg/day (Franklin et al. 2005). Franklin et al. found that as injured Washington workers were given more prescriptions of higher doses of opioids, the rates of opioid overdoses among that population jumped, from zero in 1996 to more than twenty in 2005. And in 2009, over thirty people receiving opioid prescriptions through the Workers' Compensation Program died of an opioid overdose.

107. Doctors wrote 72.4 opioid prescriptions per 100 persons in 2006. This rate increased 4.1% annually from 2006 to 2008 and 1.1% annually from 2008 to 2012. It then decreased reaching a rate of 66.5 per 100 persons in 2016. A record number of drug overdose deaths occurred in 2015: 52,404. While a death may involve more than one drug, prescription or illicit opioids were involved in 63.1% of these deaths. There was a steady increase in mortality rates for natural or semi-synthetic opioids (e.g., hydrocodone, oxycodone) from 1999 to 2010, but now has been replaced by climbing rates of heroin and especially synthetics such as fentanyl. For OD deaths involving synthetic opioids other than methadone, the rate increased from 0.3 per 100,000 in 1999 to 3.1 in 2015 ($p<0.05$) – a ten-fold increase (Annual Surveillance Report of

Drug-Related Risks and Outcomes. Centers for Disease Control and Prevention. https://www.cdc.gov/drugoverdose/pdf/pubs/2017-cdc-drug-surveillance-report.pdf, 2017).

108. Risks of dependence and addiction are greater when opioid analgesics are used long-term than when they are used short-term (Boscarino et al. 2011). Moreover, it has been shown that once patients have been on opioids longer than 90 days, the risk that they will continue on opioids chronically and for developing a substance use disorder increase (Krashin, Murinova, and Sullivan 2016). In addition to substance use disorder (Han et al. 2017), morbidity related to opioid therapy for chronic pain includes reduced testosterone, cardiac abnormalities, fractures, and immunosuppression, among other adverse outcomes (Chou et al. 2015).

109. When randomized trials and observational studies involving adults with chronic pain who were prescribed long-term opioid therapy (opioid therapy evaluated long-term (>1 year) were examined, there was insufficient evidence to determine the effectiveness of long-term opioid therapy for improving chronic pain and function. However, an opioid dose-dependent risk for serious harms was found (Chou et al. 2015). In other patient populations (veterans) associations have also been established between occasional and chronic opioid use and increased risk of hospital readmission, and risk of death (Mosher et al. 2014). A retrospective population-based cohort study conducted of opioid prescriptions given to patients with polyneuropathy, long-term opioid therapy did not improve functional status but rather was associated with a higher risk of subsequent opioid dependency and overdose. (Hoffman et al. 2017).

110. In a national sample of 1,424 people across Australia experiencing pain for a median of 10 years, greater daily OME (oral morphine equivalent) consumption was associated with higher odds of multiple physical and mental health issues, aberrant opioid use, problems associated with opioid medication and opioid dependence. Past-year dependence was

independently associated with being younger, exhibiting more aberrant behaviors and having a history of benzodiazepine dependence (Campbell et al. 2015).

111. A 2015 systematic review estimated the prevalence of opioid misuse (i.e., use of opioids in ways other than prescribed despite adverse effects) in the United States to be 21.7-29.3 percent and the prevalence of addiction or continued use despite harm to be 7.8-11.7 percent (Vowles et al. 2015). In the elderly and other patients with higher risk of cognitive impairment, opioids may result in further impairment in cognition and executive function (Schiltenwolf et al. 2014). As noted earlier, there is a risk of overdose from these drugs due to opioid-induced respiratory depression (Chou et al. 2015).

112. Of the many long-term consequences of opioid use, tolerance and opioid-induced hyperalgesia (OIH) are commonly cited as reasons for waning therapeutic effect over time. Laboratory evidence is very clear that these phenomena occur after even short periods of exposure to opioids or after exposure to large doses of opioids (Angst and Clark 2006; Trang et al. 2015; Yi and Pryzbylkowski 2015). Likewise, tolerance and OIH have been demonstrated in opioid addicts, and abnormal pain sensitivity in addicts is associated with drug craving (Ren et al. 2009). On the other hand, OIH has been shown after the short-term exposure to potent, rapidly eliminated opioids such as remifentanil in human volunteers (Angst and Clark 2006; Eisenach, Tong, and Curry 2015). Correspondingly, patients for whom remifentanil is incorporated into their surgical anesthetic seem to have higher postoperative pain levels or opioid requirements consistent with either tolerance or OIH (Fletcher and Martinez 2014; de Hoogd et al. 2016).

113. In sum: In the mid-1990s, there was nothing more than weak evidence of benefit from chronic opioid therapy. Opioids have not been shown to be effective for most common

chronic pain conditions. Instead, there is strong evidence of harms, particularly with higher doses—which are exactly the doses Defendants promoted.

4. The 2016 CDC Guideline is based on a systematic review of the evidence and highlights the misleading nature of Defendants' opioid marketing.

114. While there are many published guidelines regarding the prescription of opioids, the Centers for Disease Control and Prevention (CDC) guidelines for prescribing opioids for chronic pain are some of the most carefully constructed and influential. (Dowell, Haegerich, and Chou 2016)

115. The strength of the CDC guidelines is based on several factors including the broad range of stakeholders included in the effort, the systematic and transparent review process that was used, the inclusion of consideration of public comments, and the well-developed patient and prescriber materials that accompanied the issuance of the guidelines. In general, these guidelines urge a more conservative use of opioids. Specific conclusions tending to limit opioid use include the optimization of nonopioid therapy before a trial of opioids, the use of relatively low doses of opioids, and the recommendation to carefully follow treatment outcome and taper or discontinue opioid prescribing if the goals of therapy are not met. Further to limit dose escalation are the recommendations for the use of short-acting formulations generally having smaller dosage unit sizes and the progressive enhancement in monitoring and frequency of reevaluation has been suggested as overall doses increase.

116. The medical community recognizes the 2016 CDC Guideline as a broad standard in opioid prescribing for chronic non-cancer. It is a reasonable standard and based on a systematic review of all existing evidence. However, it is ultimately a guideline—voluntary recommendations rather than mandatory standards. The 2016 Guideline was explicitly formulated in response to the public health crisis caused by widespread prescription opioid use,

and it is intended to discourage unnecessary and excessive opioid prescribing. Based on the evidence review conducted, the CDC Guideline states, "evidence is insufficient to determine the effectiveness of long-term opioids therapy for improving chronic pain and function. Evidence supports a dose-dependent risk for serious harms." The CDC's review was informed by an earlier systematic review of the evidence on long-term opioid therapy for chronic pain (Chou et al. 2014). The Guideline strongly discourages high-dose opioid use, discourages the initiation of long-acting opioids, and strongly recommends limiting the duration of prescriptions for acute pain.

117. Since the CDC Guidelines do not establish mandatory rules as to dose and duration of therapy, they should be interpreted in a manner that does not impose sudden reduction or cessation of therapy that could be counterproductive both as to the potential for withdrawal symptoms and the possibility of patients seeking illicit opioids as an alternative. Vulnerable 'legacy patients' who have been on opioids for extended periods should be offered individualized therapy that provides for tapering consistent with the knowledge that the opioids themselves do not provide long-term efficacy in most patients, and that studies show improved pain status after tapering.

118. Notwithstanding the difficulties in implementation and the limitations of available evidence, it is my opinion that the CDC Guideline is a reasonable standard and one that incorporated input from the public (Lin et al. 2017) and is being widely applied in the medical community. The recommendations of the CDC Guideline for Prescribing Opioids for Chronic Pain are similar to those of opioid prescribing guidelines of other countries ('The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain' 2017; 'Opioids for persistent pain: summary of guidance on good practice from the British Pain Society' 2012; 'Quick Clinical

Guideline for the use of Opioids in Non-Malignant Pain' 2010). These guidelines share a common goal: to improve the quality and safety in prescribing opioids for pain management and especially chronic non-cancer pain.

D. Even for those indications for which opioids are effective such as trauma or post-operative pain, the risks of prescribing opioids are significant such that non-opioid alternatives or multimodal analgesia should be used whenever possible to reduce opioid use.

1. Surgery and Acute Pain

119. Opioids are used very commonly during and following surgery. During a surgical procedure, opioids contribute to the analgesic component of a balanced anesthetic. Often the opioids used are of high potency and short duration of action to facilitate early awake times and discharge. In addition to intravenous administration, opioids are sometimes administered intrathecally or into the epidural space to provide relatively restricted analgesic effect without exposing respiratory centers in the brainstem from systemic levels of the drugs.

120. Postoperatively opioids are used in the post-anesthesia care unit, hospital wards, and as predominantly oral medications for a period ranging from days to a month or more during the convalescent period. It remains unclear how intraoperative exposure to opioids contributes to the risk for OUD. Peri-surgical exposure to opioids may be an inciting event for the eventual development of an OUD in some patients (Sun et al. 2016). Patients with OUD (e.g., individuals on methadone maintenance) are not necessarily excluded from getting a short course of opioids for acute or acute post-operative pain. More attention has been focused—appropriately, in my opinion—on reducing opioid prescribing on discharge. Providing excessive amounts of opioids postoperatively is now discouraged, and some healthcare organizations have attempted to limit the amount of postsurgical take home opioid medication.

121. Although it is recognized that opioids have an integral role in the current practice of medicine, efforts are also underway to determine which surgical procedures and subsequent recovery can be safely achieved in the absence of opioids. For example, Summa Health System in Akron, Ohio, has drastically reduced the use of opioids in surgeries at all of its hospitals as a direct result of the opioid crisis—from using opioids in 98% of procedures in 2017 to 20% currently, with a goal of reducing that figure further to 10% or less by end of 2019. Summa Health is employing regional blocks or continuous peripheral nerve blocks in addition to a multimodal analgesia approach.[6]

122. Multimodal analgesia should be used whenever possible, including acetaminophen, NSAIDs, and non-pharmacologic therapies, to minimize opioid use. It is better to avoid opioids if there are effective alternatives. Use the lowest possible dose for the least amount of time during recovery, although higher doses and use as a first option are justified early on after injury or surgery. It is important to limit prescribing to what is actually needed, to avoid inappropriate usage, or more drug in people's medicine cabinets. After most routine surgery 3-7 days is often enough.

123. This recommendation is supported by various guidelines and sources in the medical literature, including studies demonstrating that even less than 3-7 days' worth provides adequate analgesia following many routine procedures. For example, recent literature shows that even in post-surgery settings, opioids may be unnecessary, depending on the type of surgery, as in the case of thyroid and parathyroid surgery (Shindo et al. 2018). Another study reported significant reductions in post-surgery opioid prescriptions after a new protocol was introduced: Following laparoscopic cholecystectomy, the median prescription size was 250 mg (OME),

[6] https://www news5cleveland.com/news/local-news/akron-canton-news/summa-health-eliminating-opioids-from-surgeries

while median patient use was only 30 mg. This is equivalent to receiving 50 tablets of hydrocodone/acetaminophen, 5/325 mg, and using only 6 tablets. Evidence-based prescribing guidelines reduced prescription size by 63% without increasing the need for medication refills, thereby eliminating the excessive prescription of roughly 7000 pills. Patients also reported using fewer opioids after guideline implementation. (Howard et al. 2018). Other centers are working successfully to better define and reduce opioid dosing requirements following various surgery (Hill et al. 2017; Scully et al. 2018; Hill et al. 2018). For example, the overall amount of opioids prescribed to patients after gynecologic and abdominal surgery were reduced at the time of discharge and for the entire perioperative time for opioid-naive patients without changes in pain scores, complications, or medication refill requests (Mark et al. 2018).

124. A growing challenge is the intraoperative and post-operative management of opioid-tolerant trauma and/or surgery patients. The fraction of patients chronically consuming opioids scheduled for surgery is approximately 20% (Mudumbai et al. 2016). This fraction may be even larger in the context of spine or orthopedic surgery where pain from the underlying diseases is frequently treated with opioids before operations are considered. Chronic preoperative opioid use whether medically sanctioned or abuse-related portends many difficulties. These include elevated levels of postoperative pain, high and unpredictable postoperative opioid requirements, and elevated risks of postoperative respiratory depression (Rapp, Ready, and Nessly 1995; Chan et al. 2017). Beyond these immediate risks, a quickly growing body of evidence suggests chronic opioid users experience poorer surgical outcomes than their opioid-free counterparts. Examples include limited restoration of function after joint replacement surgery, poorer quality of recovery after spine surgeries, and higher levels of persistent pain after gynecological procedures (Armaghani et al. 2014; VanDenKerkhof et al. 2012; Zywiel et al.

2011). More broadly, the anesthetic technique and other aspects of perioperative management used may influence the likelihood of developing postoperative pain (Richebe, Julien, and Brulotte 2015).

125. Estimating opioid dosing for opioid tolerant patients is often trial and error, but typically, if usual opioid dosages are ineffective, results in a graded / step-wise 30-50% increase in dose. As opposed to prior practice, current practice is to first exhaust other modalities of pain control, use of multimodal strategies, clonidine, ketamine, nerve blocks etc. However, these alternatives may not be available long term, and/or the patient may be unable to tolerate their introduction.

126. Another commonly encountered acute pain situation leading to opioid exposure is the treatment of acute injuries such as after household, sporting, or motor vehicle accidents. In these situations, limited supplies of opioids may be prescribed by emergency rooms, urgent care clinics, specialty physicians, and primary care providers. Emergency room opioid prescribing has been especially closely studied, and was observed to increase over the same time period that overall opioid prescribing increased (Maughan et al. 2015). Such prescribing can set the stage for a pattern of more chronic use. For example, the use of prescription opioids by former professional athletes is very high. In fact, interscholastic sports participants may have an elevated risk of opioid use and misuse compared to non-athletes (Veliz et al. 2015). Opioid prescribing for ED patients treated for ankle sprains are common. Although unusual in this population, prescriptions greater than 225 MME were found to be associated with higher rates of prolonged opioid use but could still fall within 5- or 7-day supply limit that is promoted for safer opioid prescribing (Delgado et al. 2018). Nevertheless, Emergency Departments and their respective

associations have developed additional opioid guidelines, in line with the CDC guidelines, for the assessment and treatment of acute and acute on chronic pain in the emergency department.[7]

127. Likewise, motor vehicle accidents, particularly severe ones, appear to lead to chronic opioid use in some patients (Zwisler et al. 2015). Opioid prescribing guidelines targeting emergency rooms and other acute care settings may to a degree reduce opioid prescribing and increase the use of measures such as urine drug screening prior to prescribing (Chen et al. 2016; del Portal et al. 2016).

128. A number of non-opioid pharmacologic treatments can be used to manage pain. There is evidence that in some circumstances, some non-opioids (e.g., NSAIDs) can be as or more effective than opioids at relieving pain. While each non-opioid alternative has its own indications and risks, some are likely to be just as if not more effective than opioids for reducing pain associated with the conditions for which they are indicated and, when used appropriately, carry lower risk of adverse outcomes.

129. Even though opioids may be effective for some people in certain situations involving acute pain, it is not true that opioids are always the most effective treatment for acute pain. For example, opioids are actually less effective for control of dynamic pain that occurs with movement. According to the Oxford Pain Group League table of analgesic efficiency for acute pain, cyclooxygenase (COX) inhibitors such as diclofenac and celecoxib have a lower "number needed to treat" (NNT)[8] than opioids in these circumstances.

[7] https://www.aaem.org/UserFiles/file/Emergency-Department-Opoid-Prescribing-Guidelines.pdf

[8] NNT or "number needed to treat" is a statistical concept that offers a measurement of the impact of a medicine or therapy by estimating the number of patients that need to be treated in order to have an impact on one person.

2. Dentistry

130. It has been estimated that dentists prescribe 12 percent of all the immediate-release opioids (hydrocodone, oxycodone), behind only family physicians (Denisco et al. 2011), although rates may have declined in recent years (Levy et al. 2015). It is my opinion that, as with prescribing opioids for acute pain and perioperative pain generally, opioid prescribing in dentistry increased as a result of the broader change in the standard of care and overall perception of low risk from opioid treatment, which allowed dentists to feel comfortable sending patients home with longer prescriptions than what would be predicted as necessary for pain relief.

131. Dentists prescribe opioids mainly for a short term to treat acute postsurgical pain. Third molar extraction, for example, is probably the most common surgical procedure performed in healthy adults. It is estimated that 3.5 million third molar extractions are operated by oral and maxillofacial surgery specialists per year (this number does not include the exactions performed by general dentists). Ibuprofen was indicated as the peripherally acting postsurgical drug of choice by 73.5 percent of the oral surgeons in one study, however, 85 percent of them almost always prescribed a centrally acting opioid alone or in combination with another analgesic agent. Hydrocodone is among the most commonly prescribed opioid by oral surgeons, with one study showing that this was usually with acetaminophen and 20 tablets are prescribed on average (Moore et al. 2006). Based on this data at least 3.5 million people with an average age of 20 years (average age for third molars extraction) may be exposed to opioids related to dental treatment (Denisco et al. 2011). Importantly, a recent study showed that a substantial proportion of adolescents and young adults are exposed to opioids through dental clinicians and these dental

prescriptions may be associated with an increased risk of subsequent opioid use and abuse (Schroeder et al. 2019).

132. Opioids also may be prescribed for dental pain in emergency departments (EDs). ED visits for a non-traumatic dental condition are concluded in 45 percent of the cases with an opioid prescription (Okunseri et al. 2014). It is important to note that non-traumatic acute dental pain can be treated with relatively simple dental procedure in the dental office. However, most EDs are not equipped, staffed, or designed to provide dental care.

133. Leftover opioids prescribed by dentists may be a concern if they are shared with friends or family members to help with apparent symptoms of pain, or for other reasons (O'Neil and Hannah 2010). Mandatory checking of prescription drug monitoring program data was shown to be effective in changing the prescription pattern for pain medications by dentists in a dental urgent care clinic in New York State (Rasubala et al. 2015). Therefore, it is recommended that opioids be prescribed only for several days following the oral surgical procedure. Although there is a paucity of literature regarding the duration of pain following oral surgery, 2-3 days' treatment is often thought to be sufficient (Biron et al. 1996). Moreover, extended severe pain after oral surgery may indicate infection or other complication and a visit to the dentist is better option than prolonged treatment with opioids or other painkillers. In addition, treatment with peripherally acting analgesic agents, such as ibuprofen and naproxen, has been shown to provide good pain relief (Moore et al. 2015) that can be as effective as opioids for many patients who undergo impacted tooth extraction (Hersh et al. 1993). Non-opioid analgesic agents such as NSAIDs may be considered the first line of therapy for the routine management of acute postoperative dental-related pains for patients who do not have contraindications to its use (Becker 2010; Donaldson and Goodchild 2010).

134. Another concern is the influence that long-term opioid users may have on opioid naïve family members. Adolescent and young adult family members of long-term opioid users had an increased risk of persistent opioid use after a subsequent surgical or dental procedure (Harbaugh et al. 2019).

3. Cancer-Related Pain and End-of-Life Care

135. The aggressive use of opioids has long been accepted and strongly promoted for the treatment of pain in patients with cancer or who are in end-of-life and palliative care. Foundational work in this area suggested that control of pain due to active cancers could be achieved using oral analgesics including opioids in most patients. Such data led to the construction of the World Health Organization "Analgesic Ladder" discussed above, which outlines the use of progressively stronger analgesics as necessary to control pain (WHO, 1986). The pain, palliative care, and oncology literatures are replete with studies of various short- and long-acting opioids used to control cancer pain, generally with positive results. It was within the contexts of cancer and palliative care that the concept of "breakthrough" pain treatment gained popularity. This in turn has supported the development of fast-acting high-potency opioid preparations such as trans-mucosal and intranasal products. Overall, the aggressive use of opioids for control of pain in cancer and palliative care patients is common and strongly supported by available literature and by the medical community (Hadley et al. 2013) (Schmidt-Hansen et al. 2015) (Wiffen, Wee, and Moore 2016) (Zeppetella and Davies 2013).

136. However, the use of opioids in these populations is not without caveats. For example, nausea, constipation, sedation, and other side effects are common after the administration of opioids in cancer pain patients just as they are in those suffering from other pain conditions. Accidental overdose can occur and patients with cancer diagnoses are subject to

increased risk of opioid mortality in a dose-response relationship, with a hazard ratio (HR) of approximately 6 at doses between 50-100 mg/day MME, and HR of approximately 12 at doses > 100 mg/day MME. Therefore, caution should be exercised in prescribing opioids to cancer patients, especially as more patients are surviving longer (Bohnert et al. 2011). Studies examining the results of urine drug screens from cancer and palliative pain patients have provided significant evidence of opioid diversion and misuse (Barclay, Owens, and Blackhall 2014; Childers, King, and Arnold 2015), while many cancer pain and palliative care clinics do not have formal policies surrounding drug misuse and diversion (Tan, Barclay, and Blackhall 2015). In addition, improperly stored or monitored medications prescribed to cancer or palliative care patients may make their way into the community.

137. An additional problem becoming more commonly recognized relates to the problem of chronic pain in cancer survivors. In addition to common non-cancer related causes, chronic pain in cancer survivors can result from the sequelae of the disease itself or treatments such as surgery, radiation, and chemotherapy. Opioids use in cancer survivors is common (Carmona-Bayonas et al. 2017). Very little data are available to quantify the frequency of opioid misuse amongst cancer survivors, but guidelines have been issued suggesting that providers use approaches similar to those employed for non-cancer paints when making decisions regarding ongoing opioid prescribing (Kurita and Sjogren 2015; Paice et al. 2016).

138. In sum, opioid use is appropriate for cancer pain from active malignant disease, as well as end-of-life pain and hospice care (defined as 6 months or less of life expectancy if disease runs normal course); however, even in these indications, opioid use is associated with risks and harm and should be balanced with a comprehensive analgesic care plan that, when appropriate, utilizes multimodal approaches.

V. CONCLUSION

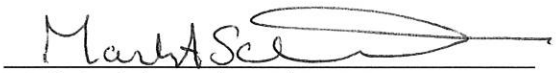
139. Chronic pain affects millions of Americans and is associated with a number of co-morbidities. While there is a pressing need to help these individuals manage their pain, long-term use of opioids has not been shown to be an effective or safe option for the treatment of chronic pain. Moreover, opioid use is associated with a number of harms, including addiction and overdose

140. The last several decades have made abundantly clear that opioids are not the answer for the vast majority of chronic pain patients. Opioids have long been used successfully for the management of acute pain (e.g., acute post-surgical and post-procedural pain), but available evidence does not support the long-term use of opioids for chronic pain management. Emphasis was appropriately placed on the need to recognize and treat of pain; however, these concerns often were not balanced with a similar emphasis on precautions to avoid adverse effects, such as development of addiction (Kolodny et al. 2015), including opioid-use disorder, opioid overdose, fractures, myocardial infarction, and others (Chou et al. 2015; Krashin, Murinova, and Sullivan 2016). Therefore, physicians increasingly prescribed opioids for chronic non-cancer pain, sometimes in very high doses, under the incorrect belief—promoted at every turn by Purdue and others—that risk for the development of substance use disorders and addiction was low (Krashin, Murinova, and Sullivan 2016).

141. Over the past decades millions of Americans have been exposed to, and many are now maintained chronically on, opioid pain medications. Many such patients have transitioned into illicit opioid markets with devastating results. Therefore, the short- and longer-term risks of opioid use are more serious than previously estimated, and the likely benefits of chronic opioid use for pain are lower for many patients than previously believed. As a result, a large group of

"legacy" chronic pain patients continue to receive opioids at doses or under circumstances that are inappropriate in light of current knowledge.

DATED March 25, 2019.



Mark A. Schumacher, PhD, MD

REFERENCES

'The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain'. 2017. *Canadian National Pain Center* *http://nationalpaincentre.mcmaster.ca/documents/Opioid%20GL%20for%20CMAJ_01may2017.pdf*.

Abdel Shaheed, C., C. G. Maher, K. A. Williams, R. Day, and A. J. McLachlan. 2016. 'Efficacy, Tolerability, and Dose-Dependent Effects of Opioid Analgesics for Low Back Pain: A Systematic Review and Meta-analysis', *JAMA Intern Med*, 176: 958-68.

Angst, M. S., and J. D. Clark. 2006. 'Opioid-induced hyperalgesia: a qualitative systematic review', *Anesthesiology*, 104: 570-87.

Armaghani, S. J., D. S. Lee, J. E. Bible, K. R. Archer, D. N. Shau, H. Kay, C. Zhang, M. J. McGirt, and C. J. Devin. 2014. 'Preoperative opioid use and its association with perioperative opioid demand and postoperative opioid independence in patients undergoing spine surgery', *Spine (Phila Pa 1976)*, 39: E1524-30.

Baker, D. W. 2017. 'History of The Joint Commission's Pain Standards: Lessons for Today's Prescription Opioid Epidemic', *JAMA*, 317: 1117-18.

Baldini, A., M. Von Korff, and E. H. Lin. 2012. 'A Review of Potential Adverse Effects of Long-Term Opioid Therapy: A Practitioner's Guide', *Prim Care Companion CNS Disord*, 14.

Ballantyne, J. C., and N. S. Shin. 2008. 'Efficacy of opioids for chronic pain: a review of the evidence', *Clin J Pain*, 24: 469-78.

Barclay, J. S., J. E. Owens, and L. J. Blackhall. 2014. 'Screening for substance abuse risk in cancer patients using the Opioid Risk Tool and urine drug screen', *Support Care Cancer*, 22: 1883-8.

Becker, D. E. 2010. 'Pain management: Part 1: Managing acute and postoperative dental pain', *Anesth Prog*, 57: 67-78; quiz 79-80.

Biron, R. T., E. V. Hersh, H. D. Barber, and R. J. Seckinger. 1996. 'A pilot investigation: post-surgical analgesic consumption by dental implant patients', *Dentistry*, 16: 12-3.

Bohnert, A. S., J. E. Logan, D. Ganoczy, and D. Dowell. 2016. 'A Detailed Exploration Into the Association of Prescribed Opioid Dosage and Overdose Deaths Among Patients With Chronic Pain', *Med Care*, 54: 435-41.

Bohnert, A. S., M. Valenstein, M. J. Bair, D. Ganoczy, J. F. McCarthy, M. A. Ilgen, and F. C. Blow. 2011. 'Association between opioid prescribing patterns and opioid overdose-related deaths', *JAMA*, 305: 1315-21.

Bonica, J. J. 1990. 'Evolution and current status of pain programs', *J Pain Symptom Manage*, 5: 368-74.

Booth, Martin. 1996. *Opium: A History*.

Boscarino, J. A., M. R. Rukstalis, S. N. Hoffman, J. J. Han, P. M. Erlich, S. Ross, G. S. Gerhard, and W. F. Stewart. 2011. 'Prevalence of prescription opioid-use disorder among chronic pain patients: comparison of the DSM-5 vs. DSM-4 diagnostic criteria', *J Addict Dis*, 30: 185-94.

Bostrom, E., M. Hammarlund-Udenaes, and U. S. Simonsson. 2008. 'Blood-brain barrier transport helps to explain discrepancies in in vivo potency between oxycodone and morphine', *Anesthesiology*, 108: 495-505.

Breivik, H., B. Collett, V. Ventafridda, R. Cohen, and D. Gallacher. 2006. 'Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment', *Eur J Pain*, 10: 287-333.

Busse, J. W., L. Wang, M. Kamaleldin, S. Craigie, J. J. Riva, L. Montoya, S. M. Mulla, L. C. Lopes, N. Vogel, E. Chen, K. Kirmayr, K. De Oliveira, L. Olivieri, A. Kaushal, L. E. Chaparro, I. Oyberman, A. Agarwal, R. Couban, L. Tsoi, T. Lam, P. O. Vandvik, S. Hsu, M. M. Bala, S. Schandelmaier, A. Scheidecker, S. Ebrahim, V. Ashoorion, Y. Rehman, P. J. Hong, S. Ross, B. C. Johnston, R. Kunz, X. Sun, N. Buckley, D. I. Sessler, and G. H. Guyatt. 2018. 'Opioids for Chronic Noncancer Pain: A Systematic Review and Meta-analysis', *JAMA*, 320: 2448-60.

Campbell, G., S. Nielsen, B. Larance, R. Bruno, R. Mattick, W. Hall, N. Lintzeris, M. Cohen, K. Smith, and L. Degenhardt. 2015. 'Pharmaceutical Opioid Use and Dependence among People Living with Chronic Pain: Associations Observed within the Pain and Opioids in Treatment (POINT) Cohort', *Pain Med*, 16: 1745-58.

Campbell, James. 1996. 'APS 1995 Presidential Address', *J of Pain*, 5: 85-88.

'Cancer pain relief, World Health Organization'. 1986. *World Health Organization*, Expert Committee on Cancer Pain Relief and Active Supportive Care, Geneva.

Carmona-Bayonas, A., P. Jimenez-Fonseca, E. Castanon, A. Ramchandani-Vaswani, R. Sanchez-Bayona, A. Custodio, D. Calvo-Temprano, and J. A. Virizuela. 2017. 'Chronic opioid therapy in long-term cancer survivors', *Clin Transl Oncol*, 19: 236-50.

Caterina, M. J., M. A. Schumacher, M. Tominaga, T. A. Rosen, J. D. Levine, and D. Julius. 1997. 'The capsaicin receptor: a heat-activated ion channel in the pain pathway', *Nature*, 389: 816-24.

CDC. 2017. 'U.S. Opioid Prescribing Rate Maps'. https://www.cdc.gov/drugoverdose/maps/rxrate-maps.html.

CDC, National Center for Health Statistics. 2018. "Wide-ranging online data for epidemiologic research (WONDER)." In. Atlanta, GA.

Chan, F. J., A. M. Schwartz, J. Wong, C. Chen, B. Tiwari, and S. J. Kim. 2017. 'Use of Chronic Methadone Before Total Knee Arthroplasty', *J Arthroplasty*, 32: 2105-07.

Chaparro, L. E., A. D. Furlan, A. Deshpande, A. Mailis-Gagnon, S. Atlas, and D. C. Turk. 2013. 'Opioids compared to placebo or other treatments for chronic low-back pain', *Cochrane Database Syst Rev*, 8: CD004959.

———. 2014. 'Opioids compared with placebo or other treatments for chronic low back pain: an update of the Cochrane Review', *Spine (Phila Pa 1976)*, 39: 556-63.

Chen, J. H., J. Hom, I. Richman, S. M. Asch, T. Podchiyska, and N. A. Johansen. 2016. 'Effect of opioid prescribing guidelines in primary care', *Medicine (Baltimore)*, 95: e4760.

Childers, J. W., L. A. King, and R. M. Arnold. 2015. 'Chronic Pain and Risk Factors for Opioid Misuse in a Palliative Care Clinic', *Am J Hosp Palliat Care*, 32: 654-9.

Chou, R., J. C. Ballantyne, G. J. Fanciullo, P. G. Fine, and C. Miaskowski. 2009. 'Research gaps on use of opioids for chronic noncancer pain: findings from a review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline', *J Pain*, 10: 147-59.

Chou, R., J. A. Turner, E. B. Devine, R. N. Hansen, S. D. Sullivan, I. Blazina, T. Dana, C. Bougatsos, and R. A. Deyo. 2015. 'The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop', *Ann Intern Med*, 162: 276-86.

Chou, Roger, Rick Deyo, Beth Devine, Ryan Hansen, Sean Sullivan, Jeffrey G Jarvik, Ian Blazina, Tracy Dana, Christina Bougatsos, and Judy Turner. 2014. 'The effectiveness and risks of long-term opioid treatment of chronic pain'.

Cicero, T. J., J. A. Inciardi, and A. Munoz. 2005. 'Trends in abuse of Oxycontin and other opioid analgesics in the United States: 2002-2004', *J Pain*, 6: 662-72.

Clauw, D. J. 2015. 'Diagnosing and treating chronic musculoskeletal pain based on the underlying mechanism(s)', *Best Pract Res Clin Rheumatol*, 29: 6-19.

Comprehensive, National, and Cancer Network. 2016. 'Adult Cancer Pain: NCCN Clinical Practice Guidelines in Oncology'. https://www.nccn.org/professionals/physician_gls/pdf/pain.pdf.

Courtwright, David T. 2001. *Dark paradise : a history of opiate addiction in America* (Harvard University Press: Cambridge, Mass.).

———. 2015. 'Preventing and Treating Narcotic Addiction — A Century of Federal Drug Control', 373: 2095-97.

Dahlhamer, J., J. Lucas, C. Zelaya, R. Nahin, S. Mackey, L. DeBar, R. Kerns, M. Von Korff, L. Porter, and C. Helmick. 2018. 'Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults - United States, 2016', *MMWR Morb Mortal Wkly Rep*, 67: 1001-06.

Dasgupta, N., M. J. Funk, S. Proescholdbell, A. Hirsch, K. M. Ribisl, and S. Marshall. 2016. 'Cohort Study of the Impact of High-Dose Opioid Analgesics on Overdose Mortality', *Pain Med*, 17: 85-98.

de Hoogd, S., S. J. Ahlers, E. P. van Dongen, E. M. van de Garde, T. A. Hamilton-Ter Brake, A. Dahan, D. Tibboel, and C. A. Knibbe. 2016. 'Is Intraoperative Remifentanil Associated With Acute or Chronic Postoperative Pain After Prolonged Surgery? An Update of the Literature', *Clin J Pain*, 32: 726-35.

DEA. 2019. 'Controlled Substance Schedules', Diversion Control Division. https://www.deadiversion.usdoj.gov/schedules/.

Deandrea, S., G. Apolone, M. Montanari, and L. Moja. 2008. 'Prevalence of undertreatment in cancer pain. A review of published literature', *Annals of Oncology*, 19: 1985-91.

del Portal, D. A., M. E. Healy, W. A. Satz, and R. M. McNamara. 2016. 'Impact of an Opioid Prescribing Guideline in the Acute Care Setting', *J Emerg Med*, 50: 21-7.

Delgado, M. K., Y. Huang, Z. Meisel, S. Hennessy, M. Yokell, D. Polsky, and J. Perrone. 2018. 'National Variation in Opioid Prescribing and Risk of Prolonged Use for Opioid-Naive Patients Treated in the Emergency Department for Ankle Sprains', *Ann Emerg Med*.

Denisco, R. C., G. A. Kenna, M. G. O'Neil, R. J. Kulich, P. A. Moore, W. T. Kane, N. R. Mehta, E. V. Hersh, and N. P. Katz. 2011. 'Prevention of prescription opioid abuse: the role of the dentist', *J Am Dent Assoc*, 142: 800-10.

Deyo, R. A., M. Von Korff, and D. Duhrkoop. 2015. 'Opioids for low back pain', *BMJ*, 350: g6380.

Donaldson, M., and J. H. Goodchild. 2010. 'Appropriate analgesic prescribing for the general dentist', *Gen Dent*, 58: 291-7; quiz 98-9.

Dowell, D., T. M. Haegerich, and R. Chou. 2016. 'CDC Guideline for Prescribing Opioids for Chronic Pain - United States, 2016', *MMWR Recomm Rep*, 65: 1-49.

Dunn, K. M., K. W. Saunders, C. M. Rutter, C. J. Banta-Green, J. O. Merrill, M. D. Sullivan, C. M. Weisner, M. J. Silverberg, C. I. Campbell, B. M. Psaty, and M. Von Korff. 2010. 'Opioid prescriptions for chronic pain and overdose: a cohort study', *Ann Intern Med*, 152: 85-92.

Edlund, M. J., B. C. Martin, A. Devries, M. Y. Fan, J. B. Braden, and M. D. Sullivan. 2010. 'Trends in use of opioids for chronic noncancer pain among individuals with mental health and substance use disorders: the TROUP study', *Clin J Pain*, 26: 1-8.

Eilers, H., L. A. Philip, P. E. Bickler, W. R. McKay, and M. A. Schumacher. 2001. 'The reversal of fentanyl-induced tolerance by administration of "small-dose" ketamine', *Anesth Analg*, 93: 213-4.

Eisenach, J. C., C. Tong, and R. S. Curry. 2015. 'Failure of intrathecal ketorolac to reduce remifentanil-induced postinfusion hyperalgesia in humans', *Pain*, 156: 81-7.

Eriksen, J., P. Sjogren, E. Bruera, O. Ekholm, and N.K. Rasmussen. 2006. 'Critical issues on opioids in chronic non-cancer pain. An epidemiological study.', *Pain*, 125: 172-9.

Fauber, J %J MedPage Today. 2011a. 'Academics profit by making the case for opioid painkillers', 3.

Fauber, John. 2011b. 'UW group ends firm funds', *Milwaukee Journal Sentinel*.

FDA. 2017. "Timeline of selected FDA activities & significant events addressing opioid misuse & abuse. ." In.

Fletcher, D., and V. Martinez. 2014. 'Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis', *Br J Anaesth*, 112: 991-1004.

Flor, H. , T. Fydrich, and D. C. Turk. 1992. 'Efficacy of multidisciplinary pain treatment centers: a meta-analytic review', *Pain*, 49: 221-30.

Foley, Kathleen M. 1985. 'The Treatment of Cancer Pain', 313: 84-95.

Franklin, G. M., J. Mai, T. Wickizer, J. A. Turner, D. Fulton-Kehoe, and L. Grant. 2005. 'Opioid dosing trends and mortality in Washington State workers' compensation, 1996-2002', *Am J Ind Med*, 48: 91-9.

Franklin, G. M., E. A. Rahman, J. A. Turner, W. E. Daniell, and D. Fulton-Kehoe. 2009. 'Opioid use for chronic low back pain: A prospective, population-based study among injured workers in Washington state, 2002-2005', *Clin J Pain*, 25: 743-51.

Franklin, G. M., B. D. Stover, J. A. Turner, D. Fulton-Kehoe, and T. M. Wickizer. 2008. 'Early opioid prescription and subsequent disability among workers with back injuries: the Disability Risk Identification Study Cohort', *Spine (Phila Pa 1976)*, 33: 199-204.

Freburger, J. K., G. M. Holmes, R. P. Agans, A. M. Jackman, J. D. Darter, A. S. Wallace, L. D. Castel, W. D. Kalsbeek, and T. S. Carey. 2009. 'The rising prevalence of chronic low back pain', *Arch Intern Med*, 169: 251-8.

'Fueling an epidemic. Exposing the financial ties between opioid manufacturers and third party advocacy groups'. 2018. *US Senate and Homeland Security & Governmental Affairs Committee, Ranking Member's Office* *https://www.hsgac.senate.gov/imo/media/doc/REPORT-Fueling%20an%20Epidemic-Exposing%20the%20Financial%20Ties%20Between%20Opioid%20Manufacturers%20and%20Third%20Party%20Advocacy%20Groups.pdf* *accessed 4/11/2018*.

Furlan, A., L. E. Chaparro, E. Irvin, and A. Mailis-Gagnon. 2011. 'A comparison between enriched and nonenriched enrollment randomized withdrawal trials of opioids for chronic noncancer pain', *Pain Res Manag*, 16: 337-51.

GAO. 2003. "Prescription Drugs: OxyContin Abuse and Diversion and Efforts to Address the Problem." In, edited by General Accounting Office.

Gaskell, H., S. Derry, C. Stannard, and R. A. Moore. 2016. 'Oxycodone for neuropathic pain in adults', *Cochrane Database Syst Rev*, 7: Cd010692.

Goldenberg, D. L., D. J. Clauw, R. E. Palmer, and A. G. Clair. 2016. 'Opioid Use in Fibromyalgia: A Cautionary Tale', *Mayo Clin Proc*, 91: 640-8.

Gomes, T., M. M. Mamdani, I. A. Dhalla, J. M. Paterson, and D. N. Juurlink. 2011. 'Opioid dose and drug-related mortality in patients with nonmalignant pain', *Arch Intern Med*, 171: 686-91.

Gran, J. T. 2003. 'The epidemiology of chronic generalized musculoskeletal pain', *Best Pract Res Clin Rheumatol*, 17: 547-61.

Greco, M. T., A. Roberto, O. Corli, S. Deandrea, E. Bandieri, S. Cavuto, and G. Apolone. 2014. 'Quality of cancer pain management: an update of a systematic review of undertreatment of patients with cancer', *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 32: 4149-54.

Guzman, J. , R. Esmail, K. Karjalainen, A. Malmivaara, E. Irvin, and C. Bombardier. 2001. 'Multidisciplinary rehabilitation for chronic low back pain: systematic review', *BMJ*, 322: 1511-6.

Haddox, J.D., D. Joranson, R.T. Angarola, A. Brady, D.B. Carr, R. Blonskey, D. Burchiel, M. Gitlin, M. Midcap, R. Payne, D. Simon, S. Vasudevan, and P. Wilson. 1997. 'The use of opioids for the treatment of chronic pain. A consensus statement from the American Academy of Pain Medicine and the American Pain Society', *pub.: American Academy of Pain Medicine and American Pain Society*.

Hadley, G., S. Derry, R. A. Moore, and P. J. Wiffen. 2013. 'Transdermal fentanyl for cancer pain', *Cochrane Database of Systematic Reviews*.

Hale, M.E., K.L. Speight, Z. Harsanyi, T. Iwan, N.S. Slagle, P.G. Lacouture, and A.C. Darke. 1997. 'Efficacy of 12 hourly controlled-release codeine compared with as required dosing of acetaminophen plus codein in patients with chronic low back pain', *Pain Res Manag*, 2: 33-38.

Han, B., W. M. Compton, C. Blanco, E. Crane, J. Lee, and C. M. Jones. 2017. 'Prescription Opioid Use, Misuse, and Use Disorders in U.S. Adults: 2015 National Survey on Drug Use and Health', *Ann Intern Med*.

Harbaugh, C. M., J. S. Lee, K. P. Chua, B. Kenney, T. J. Iwashyna, M. J. Englesbe, C. M. Brummett, A. S. Bohnert, and J. F. Waljee. 2019. 'Association Between Long-term Opioid Use in Family Members and Persistent Opioid Use After Surgery Among Adolescents and Young Adults', *JAMA Surg*: e185838.

Hedegaard H, Miniño AM, Warner M. 2018. "Drug overdose deaths in the United States, 1999–2017." In *NCHS Data Brief*, edited by National Center for Health Statistics. Hyattsville, MD

Henschke, N., S. J. Kamper, and C. G. Maher. 2015. 'The epidemiology and economic consequences of pain', *Mayo Clin Proc*, 90: 139-47.

Hersh, E. V., S. Cooper, N. Betts, D. Wedell, K. MacAfee, P. Quinn, C. Lamp, G. Gaston, S. Bergman, and E. Henry. 1993. 'Single dose and multidose analgesic study of ibuprofen and meclofenamate sodium after third molar surgery', *Oral Surg Oral Med Oral Pathol*, 76: 680-7.

HHS. 2018. "Key substance use and mental health indicators in the United States: Results from the 2017 National Survey on Drug Use and Health " In, edited by Substance Abuse and Mental Health Services Administration. Rockville, MD: Center for Behavioral Health Statistics and Quality.

Hill, M. V., M. L. McMahon, R. S. Stucke, and R. J. Barth, Jr. 2017. 'Wide Variation and Excessive Dosage of Opioid Prescriptions for Common General Surgical Procedures', *Ann Surg*, 265: 709-14.

Hill, Maureen V., Ryland S. Stucke, Michelle L. McMahon, Julia L. Beeman, and Richard J. Jr. Barth. 2018. 'An Educational Intervention Decreases Opioid Prescribing After General Surgical Operations', 267: 468-72.

Hoffman, DE. 2016. 'Treating pain V.

Reducing drug diversion and abuse: Recalibrating the balance in our drug control laws and policies. ', *Saint Louis University Journal of Health Law & Policy*: 231-310.

Hoffman, E. M., J. C. Watson, J. St Sauver, N. P. Staff, and C. J. Klein. 2017. 'Association of Long-term Opioid Therapy With Functional Status, Adverse Outcomes, and Mortality Among Patients With Polyneuropathy', *JAMA Neurol*, 74: 773-79.

Howard, Ryan, Jennifer Waljee, Chad Brummett, Michael Englesbe, and Jay Lee. 2018. 'Reduction in Opioid Prescribing Through Evidence-Based Prescribing GuidelinesReduction in Opioid Prescribing Through Evidence-Based Prescribing GuidelinesLetters', *JAMA Surg*, 153: 285-87.

IMS Health, National Prescription Audit. 1997-2013. "Opioid Prescriptions Dispensed by US Retail Pharmacies, data extracted 2014." In.

Jamison, R.N., S.A. Raymond, E.A. Slawsby, S.S. Nedeljkovic, and N.P. Katz. 1998. 'Opioid therapy for chronic noncancer back pain: a randomized prospective study', *Spine*, 23: 2591-600.

Kalso, E., J. E. Edwards, R. A. Moore, and H. J. McQuay. 2004. 'Opioids in chronic non-cancer pain: systematic review of efficacy and safety', *Pain*, 112: 372-80.

Kamper, S. J., A. T. Apeldoorn, A. Chiarotto, R. J. Smeets, R. W. Ostelo, J. Guzman, and M. W. van Tulder. 2015. 'Multidisciplinary biopsychosocial rehabilitation for chronic low back pain: Cochrane systematic review and meta-analysis', *BMJ*, 350: h444.

Kolodny, A., D. T. Courtwright, C. S. Hwang, P. Kreiner, J. L. Eadie, T. W. Clark, and G. C. Alexander. 2015. 'The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction', *Annu Rev Public Health*, 36: 559-74.

Krashin, D., N. Murinova, and M. Sullivan. 2016. 'Challenges to Treatment of Chronic Pain and Addiction During the "Opioid Crisis"', *Curr Pain Headache Rep*, 20: 65.

Krebs, E. E., A. Gravely, S. Nugent, A. C. Jensen, B. DeRonne, E. S. Goldsmith, K. Kroenke, M. J. Bair, and S. Noorbaloochi. 2018. 'Effect of Opioid vs Nonopioid Medications on Pain-Related Function in Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain: The SPACE Randomized Clinical Trial', *JAMA*, 319: 872-82.

Kurita, G. P., and P. Sjogren. 2015. 'Pain management in cancer survivorship', *Acta Oncol*, 54: 629-34.

Leung, P. T. M., E. M. Macdonald, M. B. Stanbrook, I. A. Dhalla, and D. N. Juurlink. 2017. 'A 1980 Letter on the Risk of Opioid Addiction', *N Engl J Med*, 376: 2194-95.

Levine, Mark N., David L. Sackett, and Haydn Bush. 1986. 'Heroin vs Morphine for Cancer Pain?', *Archives of internal medicine*, 146: 353-56.

Levy, B., L. Paulozzi, K. A. Mack, and C. M. Jones. 2015. 'Trends in Opioid Analgesic-Prescribing Rates by Specialty, U.S., 2007-2012', *Am J Prev Med*, 49: 409-13.

Lin, D. H., E. Lucas, I. B. Murimi, A. Kolodny, and G. C. Alexander. 2017. 'Financial Conflicts of Interest and the Centers for Disease Control and Prevention's 2016 Guideline for Prescribing Opioids for Chronic Pain', *JAMA Intern Med*, 177: 427-28.

Linssen, A. C., and P. Spinhoven. 1992. 'Multimodal treatment programmes for chronic pain: a quantitative analysis of existing research data', *J Psychosom Res*, 36: 275-86.

Maier, C., J./Klinger Hildebrandt, R., C. Henrich-Eberl, and G. Lindena. 2002. 'Morphine responsiveness, efficacy and tolerability in patients with chronic non-tumor associated pain - results of a double-blind placebo-controlled trial (MONTAS)', *Pain*, 97: 223-33.

Mark, Jaron, Deanna M. Argentieri, Camille A. Gutierrez, Kayla Morrell, Kevin Eng, Alan D. Hutson, Paul Mayor, J. Brian Szender, Kristen Starbuck, Sarah Lynam, Bonnie Blum, Stacey Akers, Shashikant Lele, Gyorgy Paragh, Kunle Odunsi, Oscar de Leon-Casasola, Peter J. Frederick, and Emese Zsiros. 2018. 'Ultrarestrictive Opioid Prescription Protocol for Pain Management After Gynecologic and Abdominal SurgeryOpioid Protocol for Pain Management After Gynecologic and Abdominal SurgeryOpioid Protocol for Pain Management After Gynecologic and Abdominal Surgery', *JAMA Network Open*, 1: e185452-e52.

Marks, R. M., and E. J. Sachar. 1973. 'Undertreatment of medical inpatients with narcotic analgesics', *Ann Intern Med*, 78: 173-81.

Maughan, B. C., M. A. Bachhuber, N. Mitra, and J. L. Starrels. 2015. 'Prescription monitoring programs and emergency department visits involving opioids, 2004-2011', *Drug Alcohol Depend*, 156: 282-88.

McNicol, E. D., A. Midbari, and E. Eisenberg. 2013. 'Opioids for neuropathic pain', *Cochrane Database Syst Rev*: Cd006146.

Meldrum, M. L. 2003. 'A capsule history of pain management', *JAMA*, 290: 2470-5.

———. 2016. 'The Ongoing Opioid Prescription Epidemic: Historical Context', *Am J Public Health*, 106: 1365-6.

Meske, D. S., O. D. Lawal, H. Elder, V. Langberg, F. Paillard, and N. Katz. 2018. 'Efficacy of opioids versus placebo in chronic pain: a systematic review and meta-analysis of enriched enrollment randomized withdrawal trials', *J Pain Res*, 11: 923-34.

Mezei, L., and B. B. Murinson. 2011. 'Pain education in North American medical schools', *J Pain*, 12: 1199-208.

Moore, P. A., H. S. Nahouraii, J. G. Zovko, and S. R. Wisniewski. 2006. 'Dental therapeutic practice patterns in the U.S. II. Analgesics, corticosteroids, and antibiotics', *Gen Dent*, 54: 201-7; quiz 08, 21-2.

Moore, R. A., P. J. Wiffen, S. Derry, T. Maguire, Y. M. Roy, and L. Tyrrell. 2015. 'Non-prescription (OTC) oral analgesics for acute pain - an overview of Cochrane reviews', *Cochrane Database Syst Rev*: Cd010794.

Morgan, JP. 1985. "American opiophobia: customary underutilization of opioid analgesics." In, 163-73. Adv Alcohol Subst Abuse.

Mosher, H. J., L. Jiang, M. S. Vaughan Sarrazin, P. Cram, P. J. Kaboli, and M. W. Vander Weg. 2014. 'Prevalence and characteristics of hospitalized adults on chronic opioid therapy', *J Hosp Med*, 9: 82-7.

Mudumbai, S. C., E. M. Oliva, E. T. Lewis, J. Trafton, D. Posner, E. R. Mariano, R. S. Stafford, T. Wagner, and J. D. Clark. 2016. 'Time-to-Cessation of Postoperative Opioids: A Population-Level Analysis of the Veterans Affairs Health Care System', *Pain Med*, 17: 1732-43.

Mularski, R. A., F. White-Chu, D. Overbay, L. Miller, S. M. Asch, and L. Ganzini. 2006. 'Measuring pain as the 5th vital sign does not improve quality of pain management', *J Gen Intern Med*, 21: 607-12.

Munglani, R. 2019. 'The not so vital sign or why there is no stethoscope for pain', *Pain News*, 17: 4-7.

Musto, David F. 1999. *The American disease : origins of narcotic control* (Oxford University Press: New York).

O'Neil, M., and K. L. Hannah. 2010. 'Understanding the cultures of prescription drug abuse, misuse, addiction, and diversion', *W V Med J*, 106: 64-70.

Okie, S. 2010. 'A flood of opioids, a rising tide of deaths', *N Engl J Med*, 363: 1981-5.

Okunseri, Christopher, Elaye Okunseri, Qun Xiang, Joshua M. Thorpe, and Aniko Szabo. 2014. 'Prescription of opioid and nonopioid analgesics for dental care in emergency departments: Findings from the National Hospital Ambulatory Medical Care Survey', 74: 283-92.

Olfson, M., S. Wang, M. Iza, S. Crystal, and C. Blanco. 2013. 'National trends in the office-based prescription of schedule II opioids', *J Clin Psychiatry*, 74: 932-9.

'Opioids for persistent pain: summary of guidance on good practice from the British Pain Society'. 2012. *Br J Pain*, 6: 9-10.

Paice, J. A., R. Portenoy, C. Lacchetti, T. Campbell, A. Cheville, M. Citron, L. S. Constine, A. Cooper, P. Glare, F. Keefe, L. Koyyalagunta, M. Levy, C. Miaskowski, S. Otis-Green, P. Sloan, and E. Bruera. 2016. 'Management of Chronic Pain in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline', *J Clin Oncol*, 34: 3325-45.

Pan, G. 2016. "Challenges in assessing real world use and abuse of pain medicines. ." In, edited by FDA Science Board Meeting.

Patijn, J, JM de Rijke, MHJ van den Beuken-van Everdingen, AG Kessels, HC Schouten, and M van Kleef. 2007. 'Prevalence of pain in patients with cancer: a systematic review of the past 40 years', *Annals of Oncology*, 18: 1437-49.

Patrick, L. E. , E. M. Altmaier, and E. M. Found. 2004. 'Long-term outcomes in multidisciplinary treatment of chronic low back pain: results of a 13-year follow-up', *Spine*, 29: 850-5.

Paulozzi, L. J., E. M. Kilbourne, N. G. Shah, K. B. Nolte, H. A. Desai, M. G. Landen, W. Harvey, and L. D. Loring. 2012. 'A history of being prescribed controlled substances and risk of drug overdose death', *Pain Med*, 13: 87-95.

Pedersen, L., P. C. Borchgrevink, Riphagen, II, and O. M. Fredheim. 2014. 'Long- or short-acting opioids for chronic non-malignant pain? A qualitative systematic review', *Acta Anaesthesiol Scand*, 58: 390-401.

Portenoy, R. K. , J. T. Farrar, M. M. Backonja, C. S. Cleeland, K. Yang, M. Friedman, S. V. Colucci, and P. Richards. 2007. 'Long-term use of controlled-release oxycodone for noncancer pain: results of a 3-year registry study', *Clin J Pain*, 23: 287-99.

Portenoy, R. K., and K. M. Foley. 1986. 'Chronic use of opioid analgesics in non-malignant pain: report of 38 cases', *Pain*, 25: 171-86.

Portenoy, R. K., D. E. Moulin, A. Rogers, C. E. Inturrisi, and K. M. Foley. 1986. 'I.v. infusion of opioids for cancer pain: clinical review and guidelines for use', *Cancer treatment reports*, 70: 575-81.

Porter, J., and H. Jick. 1980. 'Addiction rare in patients treated with narcotics (letter)', *N Engl J Med*, 302: 123.

Qaseem, A., T. J. Wilt, R. M. McLean, and M. A. Forciea. 2017. 'Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians', *Ann Intern Med*, 166: 514-30.

'Quick Clinical Guideline for the use of Opioids in Non-Malignant Pain'. 2010. *Government of Western Australia, Drug and Alcohol Office* https://www.health.qld.gov.au/__data/assets/pdf_file/0032/374693/ddu_quick_guide.pdf.

R. Bonnie, M. Ford, J. Phillips (ed.)^(eds.). 2017. *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use* (The National Academies Press: Washington DC).

Rapp, S.E., L.B. Ready, and M.L. Nessly. 1995. 'Acute pain management in patients with prior opioid consumption: a case-controlled retrospective review', *Pain*, 61: 195-201.

Rasubala, L., L. Pernapati, X. Velasquez, J. Burk, and Y. F. Ren. 2015. 'Impact of a Mandatory Prescription Drug Monitoring Program on Prescription of Opioid Analgesics by Dentists', *PLoS One*, 10: e0135957.

Remillard, D., A. D. Kaye, and H. McAnally. 2019. 'Oxycodone's Unparalleled Addictive Potential: Is it Time for a Moratorium?', *Curr Pain Headache Rep*, 23: 15.

Ren, Z. Y., J. Shi, D. H. Epstein, J. Wang, and L. Lu. 2009. 'Abnormal pain response in pain-sensitive opiate addicts after prolonged abstinence predicts increased drug craving', *Psychopharmacology (Berl)*, 204: 423-9.

Richebe, P., M. Julien, and V. Brulotte. 2015. 'Potential strategies for preventing chronic postoperative pain: a practical approach: Continuing Professional Development', *Can J Anaesth*, 62: 1329-41.

Roberts, A. H., R. A. Sternbach, and J. Polich. 1993. 'Behavioral management of chronic pain and excess disability: long-term follow-up of an outpatient program', *The Clinical journal of pain*, 9: 41-8.

Roth, S. H., R. M. Fleischmann, F. X. Burch, F. Dietz, B. Bockow, R. J. Rapoport, J. Rutstein, and P. G. Lacouture. 2000. 'Around-the-clock, controlled-release oxycodone therapy for osteoarthritis-related pain: placebo-controlled trial and long-term evaluation', *Arch Intern Med*, 160: 853-60.

Rudd, R. A., P. Seth, F. David, and L. Scholl. 2016. 'Increases in Drug and Opioid-Involved Overdose Deaths - United States, 2010-2015', *MMWR Morb Mortal Wkly Rep*, 65: 1445-52.

Saper, J. R., and A. E. Lake, 3rd. 2008. 'Continuous opioid therapy (COT) is rarely advisable for refractory chronic daily headache: limited efficacy, risks, and proposed guidelines', *Headache*, 48: 838-49.

Schatman, ME. 2010. 'Interdisciplinary chronic pain management: perspectives on history, current status, and future viability.' in J Ballantyne SM Fishman, J Rathmell (ed.), *Bonica's Management of Pain.* (Lippincott Williams & Wilkins: Baltimore, MD).

Schiltenwolf, M., M. Akbar, A. Hug, U. Pfuller, S. Gantz, E. Neubauer, H. Flor, and H. Wang. 2014. 'Evidence of specific cognitive deficits in patients with chronic low back pain under long-term substitution treatment of opioids', *Pain Physician*, 17: 9-20.

Schmidt-Hansen, M., M. I. Bennett, S. Arnold, N. Bromham, and J. S. Hilgart. 2015. 'Oxycodone for cancer-related pain', *Cochrane Database Syst Rev*: Cd003870.

Scholl, L., P. Seth, M. Kariisa, N. Wilson, and G. Baldwin. 2018. "Drug and Opioid-Involved Overdose Deaths – United States, 2013-2017." In.: Morb Mortal Wkly Rep. ePub.

Schroeder, Alan R., Melody Dehghan, Thomas B. Newman, Jason P. Bentley, and K. T. Park. 2019. 'Association of Opioid Prescriptions From Dental Clinicians for US Adolescents and Young Adults With Subsequent Opioid Use and AbuseDental Clinician–Prescribed Opioids for Adolescents and Young Adults and Subsequent Substance AbuseDental

Clinician–Prescribed Opioids for Adolescents and Young Adults and Subsequent Substance Abuse', *JAMA Intern Med*, 179: 145-52.

Scully, R. E., A. J. Schoenfeld, W. Jiang, S. Lipsitz, M. A. Chaudhary, P. A. Learn, T. Koehlmoos, A. H. Haider, and L. L. Nguyen. 2018. 'Defining Optimal Length of Opioid Pain Medication Prescription After Common Surgical Procedures', *JAMA Surg*, 153: 37-43.

Seth, Puja, Rose A. Rudd, Rita K. Noonan, and Tamara M. Haegerich. 2018. 'Quantifying the Epidemic of Prescription Opioid Overdose Deaths', 108: 500-02.

Sheehan, Kayla, Jessica Lee, Jillian Chong, Kathryn Zavala, Manohar Sharma, Sjaak Philipsen, Tomoyuki Maruyama, Zheyun Xu, Zhonghui Guan, Helge Eilers, Tomoyuki Kawamata, and Mark Schumacher. 2019. 'Transcription factor Sp4 is required for hyperalgesic state persistence', *PLoS One*, 14: e0211349.

Shindo, M., J. Lim, E. Leon, L. Moneta, R. Li, and L. Quintinalla-Diek. 2018. 'Opioid Prescribing Practice and Needs in Thyroid and Parathyroid Surgery', *JAMA Otolaryngol Head Neck Surg*.

Sjogren, P., M. Gronbaek, V. Peuckmann, and O. Ekholm. 2010. 'A population-based cohort study on chronic pain: the role of opioids', *Clin J Pain*, 26: 763-9.

Sluka, K. A., and D. J. Clauw. 2016. 'Neurobiology of fibromyalgia and chronic widespread pain', *Neuroscience*.

Sun, E. C., B. D. Darnall, L. C. Baker, and S. Mackey. 2016. 'Incidence of and Risk Factors for Chronic Opioid Use Among Opioid-Naive Patients in the Postoperative Period', *JAMA Intern Med*, 176: 1286-93.

Tan, P. D., J. S. Barclay, and L. J. Blackhall. 2015. 'Do Palliative Care Clinics Screen for Substance Abuse and Diversion? Results of a National Survey', *J Palliat Med*, 18: 752-7.

Tompkins, D. A., J. G. Hobelmann, and P. Compton. 2017. 'Providing chronic pain management in the "Fifth Vital Sign" Era: Historical and treatment perspectives on a modern-day medical dilemma', *Drug Alcohol Depend*, 173 Suppl 1: S11-s21.

Trang, T., R. Al-Hasani, D. Salvemini, M. W. Salter, H. Gutstein, and C. M. Cahill. 2015. 'Pain and Poppies: The Good, the Bad, and the Ugly of Opioid Analgesics', *J Neurosci*, 35: 13879-88.

Turk, D. C. 2002. 'Clinical effectiveness and cost-effectiveness of treatments for patients with chronic pain', *Clin J Pain*, 18: 355-65.

Turk, Dennis C., and Akiko Okifuji. 1998. 'Treatment of Chronic Pain Patients: Clinical Outcomes, Cost-Effectiveness, and Cost-Benefits of Multidisciplinary Pain Centers', 10: 181-208.

Van Zee, A. 2009. 'The promotion and marketing of oxycontin: commercial triumph, public health tragedy', *Am J Public Health*, 99: 221-7.

VanDenKerkhof, E. G., W. M. Hopman, D. H. Goldstein, R. A. Wilson, T. E. Towheed, M. Lam, M. B. Harrison, M. L. Reitsma, S. L. Johnston, J. D. Medd, and I. Gilron. 2012. 'Impact of perioperative pain intensity, pain qualities, and opioid use on chronic pain after surgery: a prospective cohort study', *Reg Anesth Pain Med*, 37: 19-27.

Vander Weele, C. M., K. A. Porter-Stransky, O. S. Mabrouk, V. Lovic, B. F. Singer, R. T. Kennedy, and B. J. Aragona. 2014. 'Rapid dopamine transmission within the nucleus accumbens: dramatic difference between morphine and oxycodone delivery', *Eur J Neurosci*, 40: 3041-54.

Veliz, P., Q. Epstein-Ngo, E. Austic, C. Boyd, and S. E. McCabe. 2015. 'Opioid use among interscholastic sports participants: an exploratory study from a sample of college students', *Res Q Exerc Sport*, 86: 205-11.

'Vital signs: overdoses of prescription opioid pain relievers - United States, 1999-2008'. 2011. *Morbidity and Mortality Weekly Report (MMWR)* *www.cdc.gov/mmwr/preview/mmwrhtml/mm6043a4.htm*.

Von Korff, Michael. 2013. 'Opioids for chronic musculoskeletal pain: Putting patient safety first', 154: 2583-85.

Vowles, K. E., M. L. McEntee, P. S. Julnes, T. Frohe, J. P. Ney, and D. N. van der Goes. 2015. 'Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis', *Pain*, 156: 569-76.

Wiffen, P. J., B. Wee, and R. A. Moore. 2016. 'Oral morphine for cancer pain', *Cochrane Database of Systematic Reviews*.

Yi, P., and P. Pryzbylkowski. 2015. 'Opioid Induced Hyperalgesia', *Pain Med*, 16 Suppl 1: S32-6.

Zedler, B., L. Xie, L. Wang, A. Joyce, C. Vick, F. Kariburyo, P. Rajan, O. Baser, and L. Murrelle. 2014. 'Risk Factors for Serious Prescription Opioid-Related Toxicity or Overdose among Veterans Health Administration Patients', *Pain Med*.

Zenz, M., and A. Willweber-Strumpf. 1993. 'Opiophobia and cancer pain in Europe', *Lancet*, 341: 1075-6.

Zeppetella, G., and A. N. Davies. 2013. 'Opioids for the management of breakthrough pain in cancer patients', *Cochrane Database Syst Rev*: Cd004311.

Zwisler, S. T., J. Hallas, M. S. Larsen, G. Handberg, S. Mikkelsen, and T. P. Enggaard. 2015. 'Opioid prescriptions before and after high-energy trauma', *J Opioid Manag*, 11: 313-8.

Zywiel, M. G., D. A. Stroh, S. Y. Lee, P. M. Bonutti, and M. A. Mont. 2011. 'Chronic opioid use prior to total knee arthroplasty', *J Bone Joint Surg Am*, 93: 1988-93.

Exhibit A

(Examples of promotional statements or materials used by Defendants in which the risk of addiction is downplayed, and the benefits to patients exaggerated)

1. Sales training and promotional materials communicating misleading information about the risk of addiction and benefits of chronic opioid use

1.1. SHC-000026573 at 2, Sales Representative Notes, (undated sales force training materials outlining answers to potential questions from physicians):

9. (Using the ladder) "How would you feel about using a drug with:
a, the same indication as Vicodin and Ultram on the low end
b. with q12h dosing and **low abuse potential**
C. as your first pain medication after NSAIDs?

10. (Using the ladder): "How comfortable would you be initiating analgesic therapy after NSAIDS with a dosing regimen more mild than Tylenol #3 dosed q 4h, and **with a low abuse potential**?"

11. (Using the PDB page 24 Figure 7) "Doctor, that's excellent that you are concerned about abuse, that's exactly why the experts are using OxyContin .... take a look at this graph...**which drug do you think is most likely to lead to abuse potential, the one that dumps all the drug within the first hour causing this spike, or the one the enter the blood stream slowly and smoothly**?"

12. (Using the PDB page 7, last sentence in first paragraph) "Doctor, how do you feel about this statement...do your patients really set their alarm docks at midnight and 4 am? How would you feel if you could prevent this and give the patient pain prevention with **minimum abuse potential**?"

13. "Doctor, Mr. Wil Corbitt, diversion program coordinator for the DEA in the state of Florida, spoke to our group in November 1997. What do you think he said is the biggest street abused drug in Florida? (answer: hydrocodone)...How would you feel about using a pain management toot that, according to the FDA, may have a **reduced abuse potential**?
…
15. "I am worded about my patient becoming dependent on OxyContin (or drugs like it)?" Ask the doctor, "Now do you mean dependent?" Introduce new visual aid and proper definitions Doctor, that's exactly why you should use OxyContin. Show APS page 26 ...risk of iatrogenic addiction is rare show blood levels on page 7 of PDB —Doctor, **which blood level do you think would be more likely to lead to abuse**??
…
26. If there were a pain medication that could provide 96.5% success right after NSAIDs, **with a reduced abuse liability**, how would you feel about

using this product? (show package insert or product data brochure validating this success rate)

…
30. Doctor, how would you feel if one pain medication could control moderate pain right after NSAIDs as well as severe pain with a 96.S% success rate and **a reduced abuse potential**?

1.2 PKY180261022 at 6, (January 2000 training materials, including pamphlet that described OxyContin as "[i]mprov[ing] quality of life, mood, and sleep.").

1.3 SHC-000004120 at 33 (OxyContin marketing War Book noting "low incidence of addiction or tolerance").

1.4 PKY180117076 at 11 (August 4, 1998 sample letter to doctors distributed to entire sales force stating "the risk of addiction to opioids in clinical care has been greatly exaggerated" and "[v]ery few patients taking opioids for pain fit this definition," and instructing doctors to "look at the facts"—noting, specifically:

[A] survey of more than 11,000 opioid-using patients, taken over several years, found that less than 1% (4 cases) of these patients had documented cases of addiction.
. . .
The risk of opioid abuse or addiction in patients without prior histories of abuse is extremely rare . . .

We're confident that effective pain management can be achieved in more patients if physicians like yourself look at the facts. By recognizing the fear of addiction, more and more patients can be helped with opioid therapy.")
(the "facts are taken from the Porter and Jick letter published by the New England Journal of Medicine in 1980 that provided no information on opioid dose, number of doses, the duration of opioid treatment, the extent of any long-term follow-up of patients, including whether opioid treatment was continued, nor the criteria used to ascertain opioid addiction).

1.5 PKY180112501 at 11, 1997 Partners Against Pain Brochure, ("[i]n fact, a survey of more than 11,000 opioid-using patients, taken over several years, found only four cases of documented addiction … Many patients—and family members—will be surprised to discover that fewer than 1% of opioid-using patients become addicted!").

1.6 ALLERGAN_MDL_00020454 at 47 ("KADIAN patients experience sustained morphine release with less fluctuations vs. morphine sulfate[;] "KADIAN patients report improved management of pain vs. morphine sulfate[;] KADIAN patients require less rescue medication vs. morphine sulfate.").

1.7 ALLERGAN_MDL_00001525 at 21 ("Kadian provides steady blood levels of morphine sulfate with few peaks and valleys.")

1.8 KP360_OHIOMDL_000027041 at 8 (A December 2007 NIPC *Pain Management Today* newsletter told healthcare providers: "[p]atients are also concerned with being looked upon as 'druggies' even though risk of addiction in the general population treated with chronic opioid therapy is extremely low. This adds to the psychological issues that often accompany chronic pain conditions.")

1.9 CHI_000435580 at 9 (A 2002 *Pain Action Guide* published by the American Pain Foundation (APF), which Endo provided with substantial financial assistance) ("Pain medications rarely cause addiction . . . Unless you have a history of substance abuse, there is little risk of addiction when these medications are properly prescribed by a doctor and taken as directed.").

1.10 JAN-MS-03090610 at 2 (Janssen unbranded website, prescriberesponsibly.com., article entitled "Use of Opioid Analgesics in Pain Management," by Keith Candiotti) ("Aside from medical issues related to opioid analgesics, there are nonmedical issues that may have an impact on prescribing patterns and patient use of these drugs. Practitioners are often concerned about prescribing opioid analgesics due to potential legal issues and questions of addiction. By the same token, patients report similar concerns about developing an addiction to opioid analgesics. While these concerns are not without some merit, it would appear that they are often overestimated. According to clinical opinion polls, true addiction occurs only in a small percentage of patients with chronic pain who receive chronic opioid analgesics analgesic therapy.").

1.11 Galer, Bradley S., Argoff, Charles E., (2010), *Defeat Chronic Pain Now!*, p. 176-178, (Mallinckrodt, through the CARES Alliance, sponsored *Defeat Chronic Pain Now*! by Bradley Galer and Charles Argoff.) (p. 176 - "When chronic pain patients take opioids to treat their pain, they rare develop a true addiction and drug craving.")' (p. 177 - "The bottom line: Only rarely does opioid medication cause a true addiction when prescribed appropriately to a chronic pain patient who does not have a prior history of addiction. (p.178 - "Here are the facts. It is very uncommon for a person with chronic pain to become 'addicted' to narcotics IF (1) he doesn't have a prior history of any addiction and (2) he only takes the medication to treat pain.").

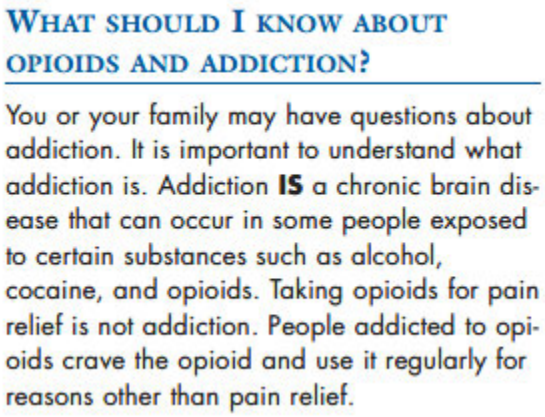
1.12 PKY180989588 at 10, "In fact, the rate of addiction amongst pain patients who are treated by doctors is much less than 1%." --- Video transcript of Purdue promotional video, featuring Dr. Alan Spanos (2000).

1.13 PURCHI-000674082 at 11, "Fact: Fears about psychological dependence are exaggerated when treating appropriate pain patients with opioids." --- Purdue Professional Sales Aid – Myths about Opioids (2001).

1.14 PURCHI-000674082 at 11, "Addiction risk also appears to be low when opioids are dosed properly for chronic, noncancer pain." --- Purdue Professional Sales Aid – Myths about Opioids (2001).

1.15 PKY180121679 at 7, "Aren't opioid pain medications like OxyContin Tablets 'addicting'? Even my family is concerned about this. … Drug addiction means using a drug to get 'high' rather than to relieve pain. You are taking opioid pain medication for medical purposes. The medical purposes are clear and the effects are beneficial, not harmful." --- Purdue patient brochure, A Guide to Your New Pain Medicine and How to Become a Partner Against Pain (1999).

1.16 ENDO-CHI_LIT-00084049 at 3, "Pain relief is an important medical reason to take opioids as prescribed by your doctor. Addicts take opioids for other reasons, such as unbearable emotional problems. Taking opioids as prescribed for pain relief is not addiction." --- Endo brochure, Understanding Your Pain: Taking Oral Opioid Analgesics (2004).



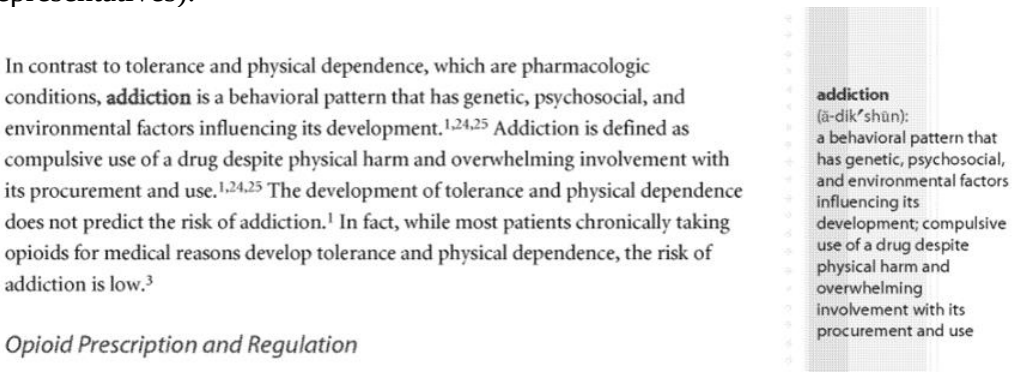
WHAT SHOULD I KNOW ABOUT OPIOIDS AND ADDICTION?

You or your family may have questions about addiction. It is important to understand what addiction is. Addiction **IS** a chronic brain disease that can occur in some people exposed to certain substances such as alcohol, cocaine, and opioids. Taking opioids for pain relief is not addiction. People addicted to opioids crave the opioid and use it regularly for reasons other than pain relief.

1.17 JAN00222151 at 89, "Addiction is relatively rare when patients take opioids appropriately." --- Janssen, Duragesic website (2006).

1.18 JAN-MS-00930135 at 13 (2009); JAN-MS-03090610 at 2 (2014), "While these concerns [about opioid addiction] are not without some merit, it would appear that they are often overestimated. According to clinical opinion polls, true addiction occurs only in a small percentage of patients." --- Janssen website, *PrescribeResponsibly.com* (last modified 2015).

1.19 MNK-T1_0001161164 at 29, Mallinckrodt, Exalgo Learning System (training for sales representatives):



In contrast to tolerance and physical dependence, which are pharmacologic conditions, **addiction** is a behavioral pattern that has genetic, psychosocial, and environmental factors influencing its development.[1,24,25] Addiction is defined as compulsive use of a drug despite physical harm and overwhelming involvement with its procurement and use.[1,24,25] The development of tolerance and physical dependence does not predict the risk of addiction.[1] In fact, while most patients chronically taking opioids for medical reasons develop tolerance and physical dependence, the risk of addiction is low.[3]

Opioid Prescription and Regulation

addiction
(ă-dik′shŭn):
a behavioral pattern that has genetic, psychosocial, and environmental factors influencing its development; compulsive use of a drug despite physical harm and overwhelming involvement with its procurement and use

1.20 JAN-MS-00303825 at 3, Janssen, Duragesic press kit:

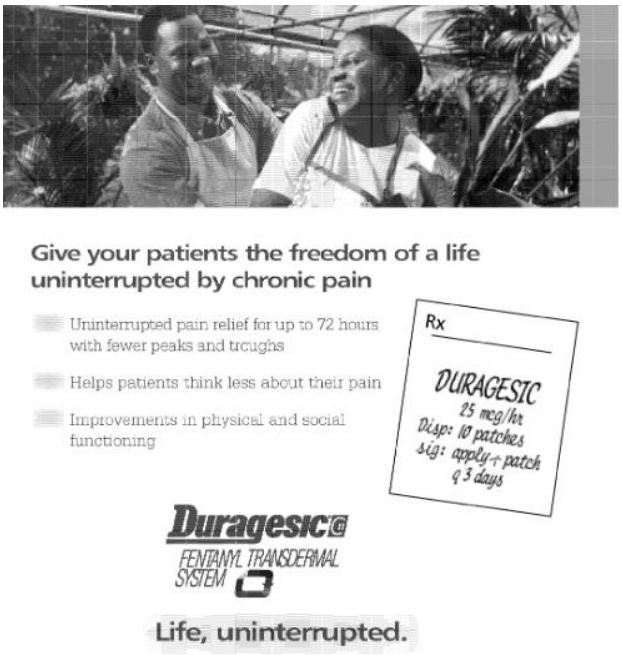
- According to the *Consensus Document* referenced above, studies indicate that the de novo development of addiction when opioids are used for the relief of pain is low.[10]

1.21 JAN-MS-00476773 at 10, "Myth: Opioids make it harder to function normally. Fact: When used correctly for appropriate conditions, opioids may make it easier for people to live normally." --- Janssen patient guide, Finding Relief: Pain Management for Older Adults (2008).

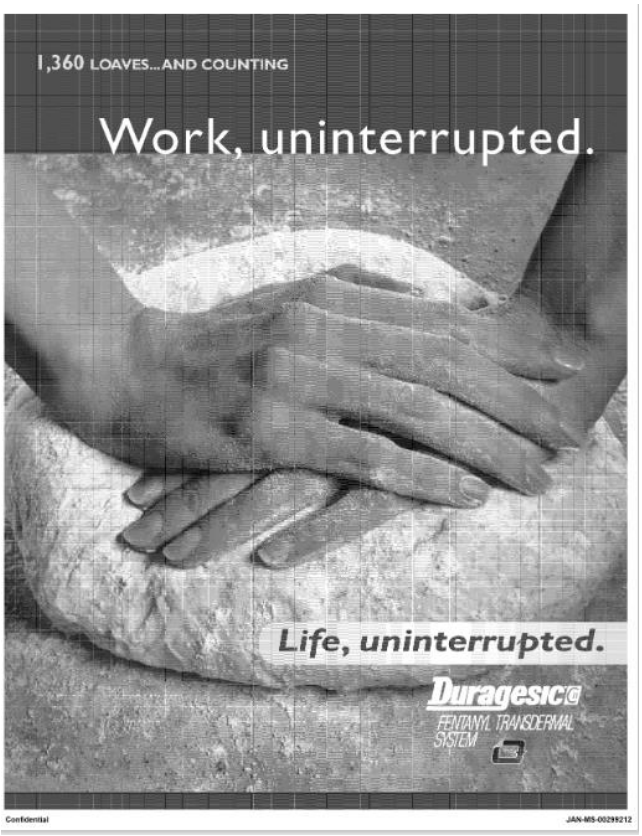
1.22 American Pain Foundation, *A Policymaker's Guide to Understanding Pain & Its Management* at 29 (2011), Dkt # 1-33, *County of Wayne, et al. v. Purdue Pharma L.P., et al.*, No. 17-cv-13334 (E.D. MI), "Multiple clinical studies have shown that long-acting opioids, in particular, are effective in improving: Daily function, Psychological health, Overall health-related quality of life for people with chronic pain."

1.23 PDD1501614879 at 3, Purdue 2006 ad for OxyContin, "There can be life with relief":

1.24 JAN-MS-00306286 at 8.



1.25 JAN-MS-00299212 at 1 (2004).



1.26 JAN-MS-00508566 at 4 (2006).

1.27 JAN-MS-00653403 at *19, Optimizing Chronic Pain Management with Duragesic, December 14, 2001. "Duragesic: A First-Line Choice for Chronic Around-the-Clock Opioid Therapy. Consider as first-line for patients with moderate-to-severe chronic pain who require continuous opioid analgesia: Degenerative joint disease; Chronic back pain; Cancer pain; Has been shown to be effective in certain cases of chronic neuropathic pain."

1.28 JAN-MS-00890573 at 1, Information About DURAGESIC® (fentanyl transdermal system), July 16, 2002, "Duragesic helps patients return to activities of daily living. In a twelve-month open-label study, Duragesic significantly improved both physical and social functioning (activities such as returning to work and participating in family life). In a crossover comparison with sustained release oral morphine, patients using Duragesic had significantly better measures of social functioning, vitality, mental health and reduced pain."

1.29 JAN-MS-00653426 at *25, Opioidphobia PowerPoint, August 1, 2001, "Iatrogenic addiction from opioid analgesia in patients experiencing pain is exquisitely rare. The Boston Collaborative Drug Surveillance Program study revealed only four cases of iatrogenic addiction among 11,882 patients without a prior history of substance abuse who received opioids for a broad range of indications."

1.30 JAN-MS-00016372 at 9, Nucynta ER Frequently Asked Questions, November 17, 2011, "In your practice you may titrate your patients at your discretion, based on your assessment of their pain management needs."

1.31 JAN-MS-00653403 at *26, Optimizing Chronic Pain Management with Duragesic, December 14, 2001, "There is no ceiling dose for opioids. Titrate the dose upward to obtain maximum pain relief without unacceptable side effects. Always prescribe rescue medication for breakthrough pain."

1.32 ALLERGAN_MDL_01052119 at 2254, Kadian Learning System(c) Alpharma Inc., "However, despite the continued unscientific beliefs of some clinicians, there is no evidence that simply taking opioids for a period of time will cause substance abuse or addiction. It appears likely that most substance-abusing patients in pain management practices had an abuse problem before entering practice."

1.33 ALLERGAN_MDL_02513506 at 10, Kadian Learning System, Chapter 5: Management of Chronic Benign Pain, ("... there is no evidence that simply taking opioids for a period of time will cause substance abuse or addiction. It appears likely that the majority of substance abusing patients in pain management practices had an abuse problem before entering the practice.")

1.34 ENDO-OPIOID_MDL-00545087 at 28, Revopan Scientific Training Module (Draft), Jan. 6, 2011, ("Studies indicate that the de novo development of addiction when opioids are used for the relief of pain is low.")

1.35 MNK-T1_000223276 at 9, Training Bulletin #21: The 411 on Pain, Sept. 25, 2006, ("Addiction to opioids is uncommon in patients who are administered these agents for pain relief.")

1.36 END00366720 at 30, Draft Training Presentation: Pain Overview by Dr. Ira Kornbluth M.D., April 17, 2009, ("Opioid addiction unlikely to develop." "If pain exists then addiction = 1:10,000")

1.37 JAN-MS-02474819 at 15-17, Continuous Pain Monograph: Management of continuous pain in the elderly, Feb. 24, 2003, [F]ear of addiction related to the use of opioids "are largely unfounded, however. Experience shows that addiction rarely arises as a consequence of opioid exposure alone, with its incidence being more strongly influenced by a wide range of psychosocial and genetic factors." (pg. 16) "Furthermore, opioid abuse is relatively uncommon in the elderly population when these drugs are appropriately prescribed." (pg. 15) "Moreover, the development of addictive behavior is extremely rare among those patients with no prior history of substance abuse." (pg. 16) "Fear of dependence has been the major barrier to the prescription of opioids, despite evidence that psychological dependence is rare in patients receiving long-term therapy for pain with opioids, with frequency estimated to be about 0.1%." (pg. 16) "It is interesting to note that, though there have been widespread increases in opioid use in recent years . . . this has not been matched by an increase in reported opioid abuses. In fact, the proportion of total drug abuse accounted for by opioid abuse fell from 5.1 to 3.8% over the same time period." (pg. 17)

1.38 PDD1501605477, Form Promotional Letter, June 26, 1998, "However, the risk of addiction to opioids In clinical care has been greatly exaggerated… In fact, a survey of more than 11,000 opioid-using patients, taken over several years, found that less than 1% (4 cases) of these patients had documented cases of addiction."

1.39 PDD1701006198 at 6, 36, Presentation: Pain Management: I hurt, therefore I suffer!, "Addiction: prevalence is less than 1% in patients with no prior history of substance abuse. Addiction is not related to physical dependence." (pg. 6) "Low incidence of addiction when purely used for pain control." (pg. 36)

1.40 PDD1701006263 at 16, Presentation: Medical and Legal Aspects of Treating Chronic Non-malignant Pain, "Addiction is not related to Physical Dependence," and "Prevalence is less than 1% in patients with no prior history of substance abuse."

1.41 SHC-000026038 at 4, Pamphlet: From One Patient to Another-Advice from patients who found relief, "Some patients may be afraid of taking opioids because they are perceived as too strong or addictive. But that is far from actual fact. Less than 1% of patients taking opioids actually become addicted."

1.42 ENDO-OPIOID_MDL-01761737 at 34, Presentation: Opioid Analgesics: A Treatment Primer, Jan. 15, 2002, "Addiction to opioids in the context of pain treatment is rare in those with no history of addictive disorders.

2. Sales training and incentives to encourage physicians to prescribe higher opioid doses.

2.1 PKY182895039, Deposition of Karen White, a sales representative for Purdue from 1998 to 2002, 98:23-99:14, Dec. 17, 2003, ("[i]t would exponentially affect our bonuses. I mean if we got the doctor, as I mentioned earlier, to write an 80 milligram instead of a 10 milligram, we would make seven and a half times more money based on what percentage of our sales that we increased over our quota."); *see* also PDD9520404001, Sposato Dep. 18:21-19:2. ("Q. My question is: Same amount of pills, higher dosage, Purdue makes more money for the higher dosage, correct? A. That's correct. Q. And that factors into someone's bonus, correct? A. Possibly.").

2.2 ENDO-OPIOID MDL-04908072 at 3 (2002 Endo "Tsunami Launch IC Plan" incentivized the Endo sales force to meet the goal of "pushing higher doses" with "rewards that increased steeply" for "deeper penetration into the high-strength [Oxy/APAP] market"—defined as Percocet 7.5/325 and 10/325 and all Oxy/APAP 7.5/500 and 10/650 variants (Percocet, Endocet, and Generic Oxycodone/APAP).

2.3 PDD1502305933, Data Review for Formularies, Nov. 1995 ("Though suitable in low doses for pain that is less severe, oxycodone is an analgesic appropriate for severe chronic pain in appropriate doses, since it has no "ceiling" for analgesic effect and may be titrated upward when clinically necessary : Deficient pain management largely stems from improper application of available knowledge concerning analgesics, especially opioids, the most effective agents for the relief of intractable pain. : One should round the dose down to one appropriate for the tablet strengths available (10, 20 and 40 mg tablets) and discontinue all other around-the-clock opioid therapy")

2.4 PKY181949492 at 5, Opioid Therapy: Consequences and Risks, April 5, 1996 ("[O]pioids may be effectively used over a prolonged period in the face of increasing dose requirements as long as intolerable side effects do not occur." and "Therefore, opioids may be used safely and effectively at even massive doses in individuals who have received gradually increasing doses over a prolonged period of time.")

2.5 PKY180112501, Counseling Your Patients and Their Families Regarding The Use of Opioids to Relieve Pain at 7, Dec. 31, 1997 ("Unlike nonopiod pain relievers, an opioid as no maximum daily does - which allows us to adjust the dose to an effective level, no matter how severe your pain.")

2.6 PKY180252074, Email re. New OxyContin 80 mg Flash Card Visual Aid, Nov. 14, 1997 ("It is important physicians understand that OXYCONTIN can be titrated on an every one-to-two day basis and there is no "ceiling" or maximum daily dose. The 80 mg tablet flash card will help us get this message out to health care providers.")

2.7 PPLPC017000008947 at 2, Debunking the Myths, Jan. 16, 2006 ("There is no upper limit to the dose of opioids that can be safely used, when the medicine is increased gradually.")

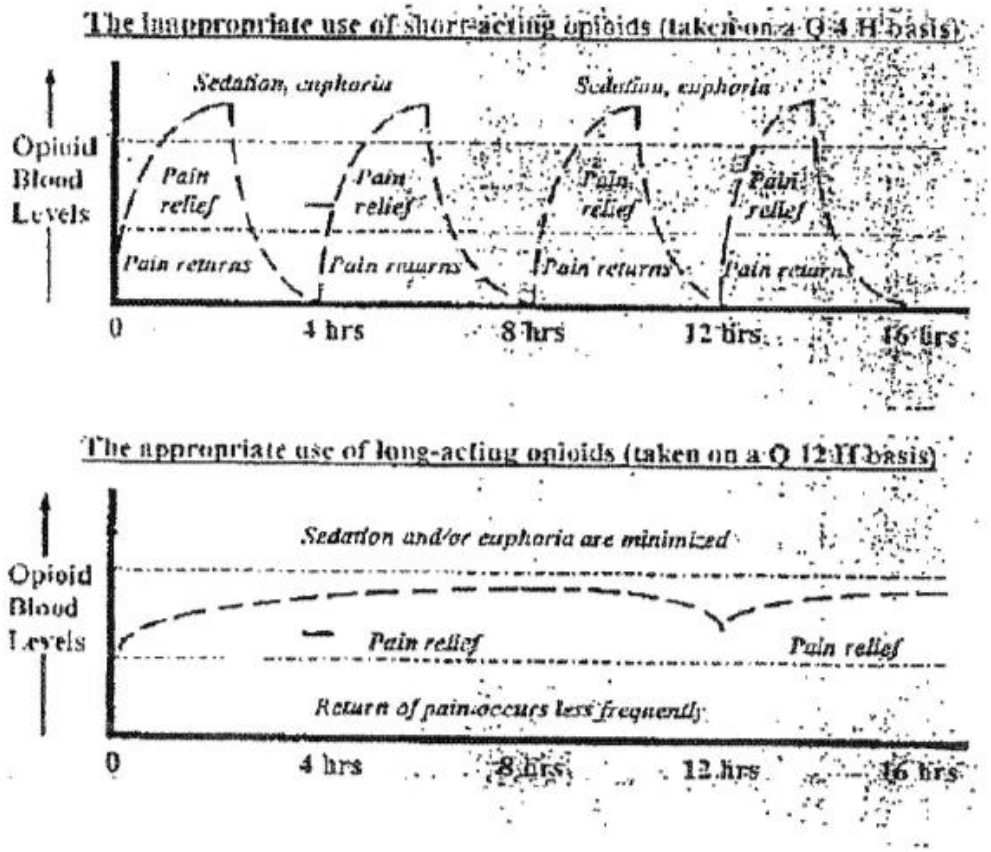
3. Documents and communications pertaining to purported 12/hr dosing and steady stage from long acting opioids)

3.1 PPLP004031668 at 39, OxyContin Focus Group Findings & Conclusions, March 8, 1995, ("**biggest negative** of the product [OxyContin] **was the abuse potential**…this was exacerbated by the fact that some felt that Q12h dosing and the lack of APAP or ASA, might make the product more susceptible to addiction.").

3.2 SHC-000020630 at 10, Haddox Letter Addendum, ("there are no data to accurately characterize the extent of addiction" among patients taking opioids").

3.3 PKY182832534, ("The idea of less abuse liability due to our controlled release matrix must be properly emphasized for proper pain patients.").

3.4 PDD1712900035 at 8, Exhibit B to Plea Agreement of *U.S. v. The Purdue Frederick Co. Inc*., Agreed Statement of Facts.


The inappropriate use of short-acting opioids (taken on a Q 4 H basis)
Opioid Blood Levels
Sedation, euphoria
Sedation, euphoria
Pain relief
Pain relief
Pain relief
Pain relief
Pain returns
Pain returns
Pain returns
Pain returns
0
4 hrs
8 hrs
12 hrs
16 hrs
The appropriate use of long-acting opioids (taken on a Q 12 H basis)
Opioid Blood Levels
Sedation and/or euphoria are minimized
Pain relief
Pain relief
Return of pain occurs less frequently
0
4 hrs
8 hrs
12 hrs
16 hrs

3.5 PDD1712900035 at 6, Exhibit B to Plea Agreement of *U.S. v. The Purdue Frederick Co. Inc*., Agreed Statement of Facts, ("OxyContin has significantly fewer 'peak and trough' blood level effects than immediate-release opioids resulting in less-euphoria and less potential for abuse than short-acting opioids.")

3.6 PPLP003996830, ("Q12h vs. Q8h Warfare," sales representatives were told, "the action of adding a dose, as opposed to increasing the Q12h dose, needs to be nipped in the bud. NOW!!." They were further advised that "the war is on – OxyContin is a true 12h product. Help the MD see that 12h is appropriate dosing for the patient controlling the pain, enhancing quality of life, even if it means using an escalating dosage and number tablets."

3.7 ACTAVIS0795954, 2012 Actavis guide: Kadian and Abuse Potential

KADIAN may be less likely to be abused by health care providers and illicit users for the following reasons[2]:

- Slow onset of action
- Lower peak plasma morphine levels than equivalent doses of other formulations of morphine
- Long duration of action
- Minimal fluctuations in peak to trough plasma levels of morphine at steady state

3.8 ACTAVIS0006930, 2005 Publication Plan. Discussion of drugs and mentions PK profiles/peaks and troughs. "Current Promotional Tagline – Kadian provides consistent pain relief without the peaks and valleys."

3.9 PURCHI-000622986, 1/11/1996 "Convenient q12 schedule won't interfere with patients daytime activities or nighttime rest, and encourages compliance." p 68

3.11 ENDO-CHI_LIT-00208241, "Opana ER protects me from pain for a full 12 hours so I can go about my daily activities."

3.12 ENDO-OR-CID-00915135, "Proven and sustained oxymorphone blood levels for a full 12 hours."

3.13 END00246672, 11/3/2010 "Opana ER – true 12-hour dosing that lasts. Only Opana ER has a true matrix for every-12-hour dosing"

Seeking a 'tail 12-hour dose in moderate to severe chronic pain patients?

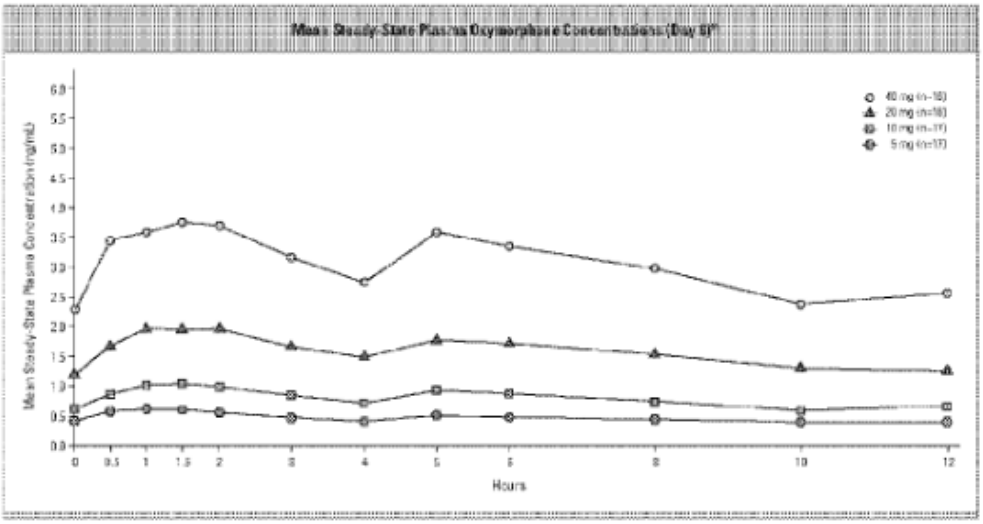
OPANA® ER: true 12-hour dosing that lasts

Only OPANA ER has a true matrix for every-12-hour dosing

- Patented TIMERx®-N oral delivery system precisely and predictably controls the release of oxymorphone into the patient's system for proven every-12-hour dosing[17]

Pharmacokinetics of OPANA ER are linear and dose proportional*[15,17]

In a randomized, 3-period, 4-sequence, crossover study in healthy volunteers[17]



Randomized, 3-period, 4-sequence, crossover study involving 24 healthy volunteers to evaluate pharmacokinetics and dose proportionality of OPANA ER. Each subject received 3 of 4 possible dose strengths (5 mg, 10 mg, 20 mg, and 40 mg) of OPANA ER. The three 1-day administration periods were seperated by a 7-day washout. On days 1 and 8, dose administration were to occur after an overnight fast. Subjects continued fasting until 4 hours after dose administration.[17]

- Steady-state levels are achieved after 3 days of multiple dose administration[1]
- Under both single-dose and steady-state conditions, dose proportionality has been established for the 5 mg, 10 mg, 20 mg, and 40 mg tablet strengths for both peak plasma levels (C_{max}) and extent of absorption (area under the curve [AUC])[2]

Long half-life of 9.4–11.3 hours[2]

***The correlation of pharmacokinetics to clinical effects has not been established.**

3.14 ENDO-CHI_LIT-00024520, Endo, *Taking a Long-Acting Opioid: What does it mean to me?* (2008)

What is the risk of becoming addicted to a long-acting opioid?

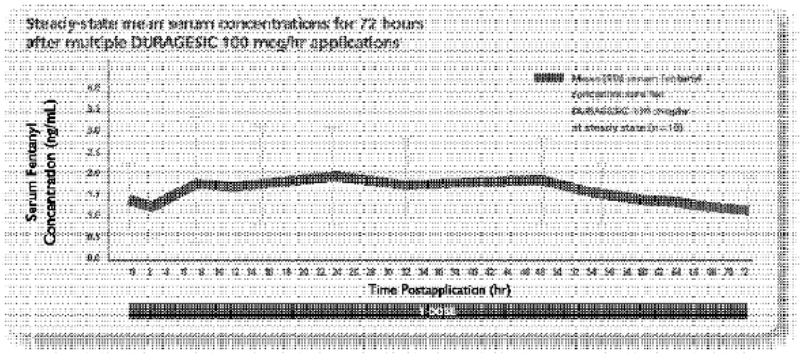
Addiction is defined as compulsive drug seeking that is beyond a person's voluntary control even if it may cause harm. Most healthcare providers who treat patients with pain agree that patients treated with prolonged opioid medicines usually do not become addicted.

3.15 JAN-MS-00299212 (2004) Duragesic

Long-lasting efficacy

Up to 72 hours of uninterrupted pain relief per patch

- Provides fewer peaks and troughs
- Consistent drug delivery over 3 days



3.16 PDD1501128421 (2003) Oxycontin

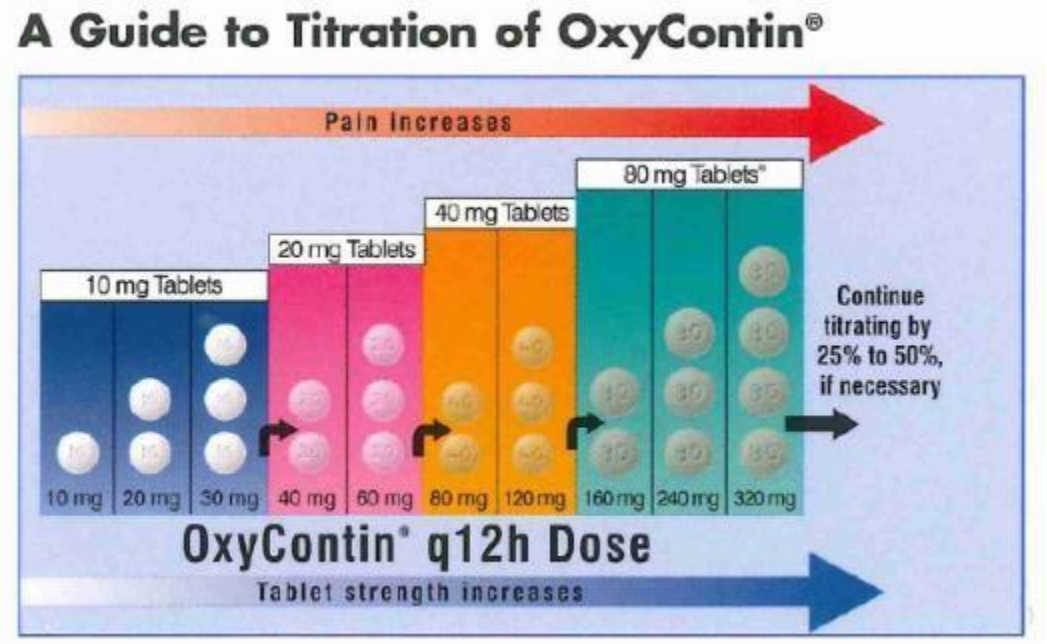


Exhibit B

(Examples of Defendants' salespeople call notes reflecting efforts to trivialize the risk of addiction and exaggerate the benefits of chronic opioid use)

1) PPLP004032436 at 45 (May 27, 1997 (Ohio – "HIT HIM ON ONSET AND LOWER ABUSE");

2) PPLPMDL0080000001 (excel spreadsheet, row 61987) (June 6, 1997 (Ohio – "GOOD OXY DISCUSSION ABOUT LOWER ABUSE POTENTIAL. SHOWED PI. CONCERNED ABOUT PUTTING AN ADDICT PAIN PATIENT ON OXY. APPRECIATED HELP. CAMERA AND WILL SEND THANK YOU.")

3) PPLPMDL0080000001 (excel spreadsheet, row 67421) (August 6, 1997 (Ohio – "DR WROTE A 20MG RX FOR A LOW BACK PATIENT WHILE IN OFFICE. ALSO GOING TO GIVE TO MUTIPLE SCLEROSIS PT. LOW ABUSE POTENTIAL, LOW TOLERANCE BUILD UP. QUICK STABLE PAIN CONTROL. NO CEILING CAN TITRATE UP")

4) PPLPMDL0080000001 (excel spreadsheet, row 76265) (November 7, 1997 (Ohio – "ALWAYS RELUCTANT TO USE NARCS BUT TOLD IF GOING TO PUT PT ON VIC/LORT OR TYL 3, WHY NOT USE THE 12 HR DOSED, WITHOUT TYLENOL AND LESS ABUSE POTENTIAL.").

5) PPLPMDL0080000001 (excel spreadsheet, row 98319) (September 18, 1998 (Ohio – "DR. HAS A TON OF VICO PTS. A LOT OF LOW BACK PAIN. LEARY OF CLASS II'S. USED PI TO SELL LOW ABUSE, Q12H, AND QOFL. DR. AGREED TO USE FOR ALL OF HIS LOW BACK INSTEAD OF VICO. KEEP ON THIS GUY, THIS IS EASY MONEY.").

6) PPLPMDL0080000001 (excel spreadsheet, row 122214) (July 6, 1999 (Ohio – "HIT OXY, DOES NOT LIKE TO PRESCRIBE NARCOS BECAUSE OF ABUSE AND ADDICTION. TURNED BOTH OBJECTIONS INTO ADV FOR OXY. DR LIKED THE FACT OF LOW ABUSE AND DRASTICALLY LESS TABS.").

7) PPLPMDL0080000001 (excel spreadsheet, row 129292) (September 20, 1999 (Ohio – "SAYS USES OXY, MOSTLY FOR NURSING HOME PATS. HE SAID HE HEARD IT NOW HAD A LOWER BACK PAIN INDICATION -- TOLD HIM STUDIES HAVE BEEN DONE FOR BACK PAIN, OSTEOARTHRITIS, AND CANCER -- DISCUSSED NO CEILING, 12HR EFFICACY, BLOOD LEVELS, LOWER ABUSE POTENTIAL. DISCUSSED FAST FOR NURSING HOME PATS.").

8) SHC-000008118 (November 19, 1997 (West Virginia) – "CONCERNED ABOUT ADDICTION WITH OPIOIDS. DIFFERENCE BETWEEN DEPENDENCE AND ADDICTION. LESS THAN 1% OF PATIENTS BECOME ADDICTED. CAN ABRUPTLY STOP LOW DOSES OF OXYCONTIN WITHOUT WITHDRAWAL SYMPTOMS.").

9) PKY182142182 (April 23, 1998 (Ohio) – "RPH WAS CONCERNED WITH THE NUMBER OF PATIENTS THAT DR RICHMOND HAS PUT ON OXY, SD THEY ARE ALL PRETTY STRANGE DIS LESS ABUSE AND ADDICTION WITH OXY AND WHY MORE APPROPRMED, DIVERSION RATE OF OXY VS OTHERS.").

10) PPLP004032436 at 80 (May 11, 1998 (Kentucky) – "USE OF FROM START TO WAS UNDER THE IMPRESSION THAT 0 WAS ONLY THERE TO REPLACE MSC. NOOOOOOO! SHOWED HIM PI INDICATION, PLUS THE NON-ADDICTIVE AND ACET PROBLEM.WHEN ILEFT HE SAID HE WAS SWITCHING THEM ALL OVER TO O FROM HYDROS WE'LL SEE.").

11) PPLP004032436 at 112 (November 4, 1998 (Kentucky) – "BEFORE.HAS A WORRY ABOUT THE DEA.TOLD HIM TO TELL THEM, IF ANYTHING EVER HAPPENED, THAT THE PURDUE REP TOLD THEM THAT IT WAS LESS ADDICTING.").

12) PPLPMDL0080000001 (excel spreadsheet, row 170276) (July 6, 2000 (Ohio) – "SPOKE WITH MD WHO EXPRESSED CONCERN RE: ONE PT RECEIVING 120 MG Q 12 FOR BACK PAIN-DISCUSSED THE PFACT THAT THERE IS NO CEILING DOSE WITH OXY LIKE SHORT ACTING; HE SEEMED TO THINK THAT THIS PT WAS ABUSING THE PRODUCT; HE NEEDS REAFFIRMATION RE: THE DECREASED ABILITY OF OXY TO BE ABUSED AND DECREASING NUMBER OF TABS….")

13) PPLPMDL0080000001 (excel spreadsheet, row 42183) (July 10, 1996 (Ohio) – "WORKING W PAM TO GET MORE PAT'S CONVERTED.THEY USE ALOT OF PERC AND THERE IS NO REASON FOR NOT USING.SLEEP AND QUALITY OF LIFE ARE IMPORTANT ISSUES AND SHOULD BE FOCUSED UPON.")

14) PLPMDL0080000001 (excel spreadsheet, row 202957) (January 19, 2001 (Ohio) – "doc said he has been using oxy for awhile and that he uses high doses, i reminded doc there is no ceiling and that he should not worry about how high he needs to go.").

15) PPLPMDL0080000001 (excel spreadsheet, row 170028) (August 11, 2000 (Ohio) – "asked r to to upgrae to the 80 mg q 12 h for difficult pat - dr. agrees - positioned oxy ir for breakthrough reminder detail to dr. on oxy - stay w message - **push the high dose** - sampled uni and senokot reminded dr that 160 mg tab is coming out - he asked

abt oxy fast for break - does not have in southside - y-town - disc high dose pat - 40 mg q 12 h asked if he would write oxy ins of … for diff pat - disc the inconsist of pain control w … - asked if he would write 80mg oxy instead of … - said he will write more oxy f **reminded dr that oxy has no ceiling** - that he can go above 80 mg - also the potency of oxy vs vic is =n asked dr what he does after 40 mg q 12 - he adds … - **explained the no ceiling of oxy - told him 60 -80mg q 12 is a low dose of a med that has no limits** - says he will go up in dose before switching - was surprised to learn that oxy is no ceiling compared to combos - asked many q about hospice pat and nurses - wanted to know what chevlen does - lots of oxy - 1--1.5 ratio less hal and naus - fu on dosing up and acute vs vic.").

16) ENDO-OPIOID_MDL-00678171 at 1-2 (October 11-12, 2006 (Charlotte District) -- Endosell Coaching Report for Brandon Myers: "Brandon, you have been very successful with Opana in your territory. . . You shared the PROMISE program with your concerned providers and reinforced that Opana ER "treats the pain and not the addiction" and shared with providers the reasons why physicians in the plain clinic are using Opana ER.")

17) ENDO-OPIOID_MDL-00678060 at 1 (October 2-3, 2006 – Endosell Coaching Report for Susan Mitchell: "I'd like you to turn up the passion some with Opana. "Stay of ahead of the pain," being "released from the grip of pain" are taglines that stand out and should be used along with the MVA. These types of statements combined with a thorough and compelling message should help you docs remember Opana better.")

18) JAN-OH-00000004 (Duragesic Sales Call Notes (Ohio) – (July 27, 1998 "LOVES DUR.REVIEWED THE NO ABUSE POTENTIAL, QUALITY OF LIFE, SAFTEY W/ GRANDCHILDEN ETC.HIT COST")

19) JAN-OH-00000004 (Duragesic Sales Call Notes (Ohio) – (August 6, 1998) "he treats chronic pain/ went over dur and uses in non mal pain specifically/ gave him a cme art/ went over pt types / no street value has had elderly pts selling theit pain meds for $$ ""dur -not just for term pt -lower back can benfit -pt more active less abuse potent.")

20) MNK-T1_0002157893 at 1 (July 15, 2010) (Email re sales message for Exalgo: "Painting a picture of the patient type for Exalgo has resonated with the physicians that have written for Exalgo. I often talk about the patient who experiences constant pain throughout the day, with only temporary relief from their immediate relief opiod. By using an extended opiod, such as Exalgo, they are able to get more sustained relief allowing them to lead a more productive life. I often cite the patient who spoke to the FDA on our behalf.")

Exhibit C

(Examples of internal Purdue communications regarding the efforts to control physician perception of OxyContin, to play on confusion regarding the strength of OxyContin and to avoid morphine stigma)

1) Interoffice Memo from Friedman to Sackler, 12/29/94, PPLP004030154 at 4-5; see also 1996 OxyC Primary Market Research, PKY180544129 at 428 (Purdue's market research anticipated that "a comfort level will be established among FPs [Family Physicians] which could expand to include OxyContin for selected non-cancer pain.").

   "If physicians perceive OxyContin as controlled-release Percocet it is likely that they will start to use it in place of oxycodone combinations. As physicians become more comfortable with use in the oxycodone combination market it is possible that they will also start to use OxyContin in place of Class III hydrocodone or codeine combination drugs….
   The port of entry to the oncology market will be oncologists and those FPs/GPs/IMs that currently treat cancer patients. By targeting both of these groups we will establish credibility in the Oncology market. The use of OxyContin in Cancer pain patients, initiated by their Oncologists and then referred back to FPs/GPs/IMs, will result in a comfort level that will enable expansion of use in chronic non-malignant pain patients also seen by the family practice specialists. As we build clinical literature and the FDA becomes more comfortable with our promotion we will be in a position to move our promotion more aggressively into the indications currently reserved for oxycodone combinations and Class III combinations, specifically post-operative pain, musculoskeletal pain, injury/trauma, and CNS pain."

2) OxyContin Investigators' Meeting, June 9-11, 1995, PKY181823986 at 17 ("among health care providers there is a perception that patients feel a 'stigma' associated with opioid analgesic therapy. Morphine and hydromorphone are most associated with this stigma. One of the patients' biggest fears appears to be the possibility of addiction…"); *see also* Minutes from Analgesia Compendium, July 15, 1992, PPLP004030121 at 2; OxyContin Project Team Minutes, June 22, 1994, PPLP004030223 at 2; PPLP004030214 at p. 9; OxyContin WarBook, 1998, SHC-000004120 at 62.

3) PKY181004545 at p. 23("there is no question that morphine has a negative stigma with patients relative to both addiction and the terminal nature of their illness."); *see also* SHC-000001965 at 2; SHC-000026456 at 46; PKY181004480 at 32; PKY181386644 at 34.

4) Friedman Email to R. Sackler, May 28, 1997, PPLP004030150 at 1 ("When we launched OxyContin, we intentionally avoided a promotional theme that would link OxyContin to cancer pain. We specifically linked OxyContin to the oxycodone combinations with our "old way, new way" campaign. We made sure that our initial detail piece provided reps with the opportunity to sell the product for a number of different pain states.").

5) Friedman Email to R. Sackler, May 28, 1997, PPLP004030150 at 1 ("it would be extremely dangerous, at this stage in the life of this product, to tamper with this 'personality,' to make physicians think the drug is stronger or equal to morphine.").

6) Email from M. Cullen, June 2, 1997, PPLP004032323 at p. 4 ("Since the non-cancer pain market is much greater than the cancer pain market, it is important that we allow this product to be positioned where it currently is in the physician's mind. If we stress the "Power of OxyContin" versus morphine, it may help us in the smaller cancer pain market, but hurt us in the larger potential non-cancer pain market. Some physicians may start positioning this product where morphine is used, and wait until pain is severe before using it…. It is important that we not change the position perception of physicians towards oxycodone when developing promotional pieces, symposia, review articles, etc..").

7) PPLP004030366 at p. 1 ("we can show that we are as 'effective' as morphine, but do not want to say OxyContin is as 'powerful' as morphine. Words such as 'powerful' may make some people think the drug is dangerous and should be reserved for the more severe pain.").

8) Friedman Email to Alfonso, Jan. 25, 2001, PPLP004030463 at p. 1 ("we were able to convince doctors to use OxyContin tablets because of its position in the doctors mind that is [sic] very different from morphine.").

9) Friedman Email to Richard Sackler, April 22, 1997, PPLP004030162 at p. 1 ("Oxycodone has a 'personality' that is influenced by many years of oxycodone use in Percocet. We have built a large part of our platform on this personality and used it to differentiate OxyContin from MS Contin and .... This differentiation has lead [sic] to much non-malignant business. Marketing is not only about what you are. It is also about what you are not. We have a success beyond our expectations that is, in part, due to the unique personality of OxyContin.").

Prepared: February 22, 2019

University of California, San Francisco

CURRICULUM VITAE

Name: Mark A. Schumacher, PhD, MD

Position: Professor, Step 4
Anesthesia & Perioperative Care
School of Medicine

Professor, Dept. of Oral and Maxillofacial Surgery

Address: Box 0427
513 Parnassus Ave, Med Sci, S436
University of California, San Francisco
San Francisco, CA 94143
Voice: 502-7022
Fax: 514-0185
Email: mark.schumacher@ucsf.edu
Web: pain.ucsf.edu

EDUCATION

1977 - 1979	University of California, San Diego	B.A	Biology
1981 - 1987	University of California, San Diego (Palmer Taylor, Theodore Friedmann)	Ph.D.	Physiology & Pharmacology
1987 - 1987	University of California, San Diego (Palmer Taylor)	Fellow	Molecular Pharmacology
1987 - 1990	University of California, San Diego	Medicine	M.D.
1990 - 1990	University of California, San Diego (Tony Yaksh)	Fellow	Pain Research
1990 - 1991	Cedars-Sinai Medical Center, Los Angeles, California	Internship	Internal Medicine
1991 - 1993	University of California, San Francisco	Residency	Anesthesia
1994 - 1995	University of California, San Francisco (Jon Levine, David Julius)	Fellow	Pain Research
2003 - 2004	Blackett Laboratory - Imperial College, London UK (Nick Franks, Mervyn Maze)	Sabbatical	Biophysics Research,

LICENSES, CERTIFICATION

1991	Diplomat, National Board of Medical Examiners
1991	California State Medical Board License No. G072778
1995	American Board of Anesthesiology

Prepared: February 22, 2019

PRINCIPAL POSITIONS HELD

1993 - 1994	University of California, San Francisco	Chief Resident	Anesthesia
1994 - 1995	University of California, San Francisco	Clinical Instructor	Anesthesia
1995 - 2001	University of California, San Francisco	Assistant Professor in Residence	Anesthesia
1995 - present	University of California, San Francisco	Attending Physician	Anesthesia
2001 - 2002	University of California, San Francisco	Associate Professor in Residence	Anesthesia
2002 - 2013	University of California, San Francisco	Associate Professor	Anesthesia
2013 - present	University of California, San Francisco	Professor	Anesthesia

OTHER POSITIONS HELD CONCURRENTLY

1995 - 2001	University of California, San Francisco	Assistant Professor in Residence	Dept. of Oral & Maxillofacial Surgery
2001 - 2002	University of California, San Francisco	Associate Professor in Residence	Dept. of Oral & Maxillofacial Surgery
2002 - 2013	University of California, San Francisco	Associate Professor	Dept. of Oral & Maxillofacial Surgery
2003 - 2004	Imperial College London, UK	Visiting Reader	
2010 - 2015	University of California, San Francisco	Medical Director	Pain Services, UCSF Medical Center
2010 - present	University of California, San Francisco	Chief	Division of Pain Medicine, Dept. of Anesthesia and Perioperative Care
2013 - present	University of California, San Francisco	Professor	Oral & Maxillofacial Surgery

HONORS AND AWARDS

1997	Radiometer/John Severinghaus Fellow in Anesthesia Research, Department of Anesthesia and Perioperative Care	University of California, San Francisco
1998	New Investigator Award	Foundation for Anesthesia Education Research (FAER)
2000	Sessler Family Anesthesia Research Award	University of California, San Francisco
2001	Frontiers in Anesthesia Research Award	International Anesthesia Research Society (IARS)

KEYWORDS/AREAS OF INTEREST

capsaicin receptor, chemotherapy induced peripheral neuropathy (CIPN), gene, genomics, Nerve Growth Factor, NGF, nociceptor, oxaliplatin, pain, promoter, splice variant, Transcription Factor - Sp1, Sp4, TRPV1, TRPA1, TRPM8, VR1.

CLINICAL ACTIVITIES

CLINICAL ACTIVITIES SUMMARY

As of January 2017, I have transitioned my clinical activity on average to 2 clinical days each week. This consists of providing approximately 8 days every month on the Anesthesia Pain Management Service, supervising residents, medical students and providing direct patient care. Previously, additional clinical activities included attending in the Moffitt Long Hospital operating rooms 1-2 days per month. Responsibilities also included in-house daytime, supervision of OR, PACU, and ICU anesthesia care plus 1 overnight E1pm/month.

PROFESSIONAL ACTIVITIES

MEMBERSHIPS

1991 - present	International Anesthesia Research Society
1991 - present	California Society of Anesthesiologists
1991 - present	American Society of Anesthesiologists
1995 - present	International Association for the Study of Pain
1995 - present	Society for Neuroscience
2000 - present	American Pain Society
2001 - present	Association of University Anesthesiologists (elected member)
2010 - 2012	World Institute of Pain

SERVICE TO PROFESSIONAL ORGANIZATIONS

1997 - 1997	IARS 71st Clinical and Scientific Congress	Co-chair, Poster Disc. Pharm

2003 - 2003	IARS 77th Clinical and Scientific Congress	Poster Moderator-Pain
2004 - 2004	IARS 78th Clinical and Scientific Congress	Poster Moderator-Pain
2010 - 2010	American Pain Society	Review National Guidelines on Management of Postoperative Pain
2015 - 2018	California Society of Anesthesiologists	Member, Task Force on Pain
2016 - 2018	The ACTTION (Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks) public-private partnership with the FDA, the American Pain Society, and the American Academy of Pain Medicine are collaborating on the development of an acute pain taxonomy with diagnostic criteria for the major acute pain conditions.	Invited Participant
2018 - 2018	Program Committee, Napa Pain Conference 2018	
2018 - 2018	Interviewed for the American Journal of Public Health January 2019 Podcast: “Pain Management: A Crisis with No End in Sight.” https://soundcloud.com/alfredomorabia/ajph-january-2019-pain-management-a-crisis-with-no-end-in-sight-english	Interviewee

SERVICE TO PROFESSIONAL PUBLICATIONS

1999 - present	Ad hoc referee, Anesthesiology
2000 - 2000	Ad hoc referee, Genomics
2000 - 2000	Ad hoc referee, Brit J Pharmacol
2000 - 2006	Ad hoc referee, Molecular Pharmacol
2002 - present	Ad hoc referee, Pain
2002 - 2002	Ad hoc referee, FEBS letters
2003 - 2006	Ad hoc referee, Brain Research
2004 - 2004	Ad hoc referee, British Medical Bulletin
2006 - present	Ad hoc referee, Neuroreport
2008 - 2008	Ad hoc referee, J Investigative Dermatology
2008 - present	Ad hoc referee, Neurosci Letters
2008 - present	Ad hoc referee, J Pain

2010 - 2010	Ad hoc referee, Stroke
2010 - 2013	Ad hoc referee, Proc Natl Acad Sci
2010 - 2012	Guest Editor, Pharmaceuticals, http://www.mdpi.com/journal/pharmaceuticals/special_issues/ion-channels/
2018 - present	Ad hoc referee, New England Journal of Medicine
2018 - present	Ad hoc referee, PLoS One

INVITED PRESENTATIONS - INTERNATIONAL

1987	Universität Bern, Institute for Biochemistry and Molecular Biology: Bern, Switzerland, May	Invited talk
1987	University of Geneve, Department of Biochemistry: Geneve, Switzerland, May	Invited talk
2002	International Association for the Study of Pain Congress: San Diego, California, August	Poster
2004	Departement Anästhesie Universitätsspital Basel: Basel, Switzerland, February	Invited talk (2)
2004	The Queen's University of Belfast, Department of Anaesthetics: Belfast Northern Ireland, June	Elected Royal College of Anaesthetists Rank Lecturer
2004	Cellular and Molecular Neuroscience Seminar Series: Imperial College, London, UK, March	Invited talk
2004	Euroanaesthesia: Lisbon, Portugal, June	Invited congress lecture
2004	World Institute of Pain: Barcelona, Spain, September	Invited talk
2004	Division of Biophysics: Imperial College London, UK, July	Invited talk
2009	World Institute of Pain: New York, New York, March	Opening plenary lecture
2011	Zambon Research Venture, Zambon Pharmaceuticals: Milan (Bresso), Italy, November	Invited talk
2011	3rd SIMPAR (Study in Multidisciplinary Pain Research) Conference: Pavia, Italy, November	Invited Moderator, Co-Chair
2012	International Association for the Study of Pain (IASP) 14th World Congress on Pain, August (The Development of Inflammatory Thermal Hyperalgesia is Dependent on Transcription Factor Sp4)	Invited talk

2013	5th SIMPAR (Study in Multidisciplinary Pain Research) Conference: Pavia, Italy, March (Mechanisms of Chronification of Acute into Chronic Pain)	Invited talk
2014	6th SIMPAR (Study in Multidisciplinary Pain Research) Conference: Rome, Italy, March (New Developments in Inflammation: TRPV1)	Invited talk
2015	7th SIMPAR (Study in Multidisciplinary Pain Research) Conference: Rome, Italy, March (Translational Mechanisms / Treatments of Lower Back Pain w/Radiculopathy)	Invited talk
2016	8th SIMPAR (Study in Multidisciplinary Pain Research) Conference: Rome, Italy, April (The Anticancer Antibiotic Mithramycin-A Inhibits TRPV1 Expression in Dorsal Root Ganglion Neurons)	Invited talk
2016	International Association for the Study of Pain (IASP), Yokohama, Japan (September, 2016)	Poster
2016	Wakayama University (October 2016)	Invited talk
2017	9th SIMPAR (Study in Multidisciplinary Pain Research) Conference: Florence, Italy, March	Invited talk
2018	International Anesthesia Research Society (IARS) 2018 Annual Meeting and International Science Symposium (April 28 – May 1). "Panel Session Number 204: A National Strategy to Reduce the Opioid Epidemic: A Report from the National Academies of Sciences, Engineering and Medicine"	Invited talk

INVITED PRESENTATIONS - NATIONAL

1995	Association of University Anesthesiologists: San Diego, California, May	Invited poster
1998	American Society of Anesthesiologists: Orlando, Florida, October	Invited poster
1999	American Pain Society: Fort Lauderdale, Florida, October	Invited poster
2000	American Society of Regional Anesthesia and Pain Medicine: Orlando, Florida, March	Invited talk
2002	International Anesthesia Research Society, Clinical and Scientific Congress: San Diego, California, April	Invited talk
2002	American Pain Society Congress: Baltimore, Maryland	Poster
2003	International Anesthesia Research Society Clinical and Scientific Congress: New Orleans, Louisiana, March	Invited talk

2003	Association of University Anesthesiologists: Milwaukee, Wisconsin, May	Invited talk
2004	International Anesthesia Research Society, Clinical and Scientific Congress: Tampa, Florida, March	Invited talk
2005	Association of University Anesthesiologists: Baltimore, Maryland, May	Poster discussion
2005	International Anesthesia Research Society, Clinical and Scientific Congress: Honolulu, Hawaii, March	Invited talk
2006	International Anesthesia Research Society, Clinical and Scientific Congress: San Francisco, California, March	Invited talk
2007	American Society of Anesthesiologists: San Francisco, California	Poster
2007	Department of Anesthesia Grand Rounds, Emory University: Atlanta, Georgia	Invited talk
2011	Association of University Anesthesiologists: Philadelphia, Pennsylvania	Invited talk
2012	American Academy of Orthopaedic Surgeons (AAOS), National Association of Orthopaedic Nurses (NAON): San Francisco, California, February (Peripheral Nerve Catheters for Postoperative Pain Control Following Total Joint Arthroplasty)	Invited talk
2012	National Institutes of Health (NIH) Pain Consortium, Centers of Excellence in Pain Education: Bethesda, Maryland, July (Interprofessional Development of Pain Education Competencies)	Invited talk
2014	American Psychosomatic Society, Mini Medical School, March (Learning from the Past to Understand the Origins of Acute to Chronic Pain)	Invited talk
2014	7th Annual Pediatric Pain Master Class, Presented by: Children's Institute for Pain and Palliative Care (CIPPC), Department of Pain Medicine, Palliative Care and Integrative Medicine, Children's Hospitals and Clinics of Minnesota, June (Integration of Multi-Modal Pain Management Into Large Health Care Setting: Challenges, Outcomes & Lessons Learned) (TRPV1 – From Bench to Bedside: Update on Current Pain Research)	Invited talk
2014	US Department of Justice, Bay Area Presciption Drug Abuse Summit, Solutions and Impact Panel (Multimodal Pain Management Strategy), May 7, San Francisco, California.	Invited talk

2015	California Society of Anesthesiologists Annual Meeting, April (How Does Acute Pain Turn Chronic?)	Invited talk
2016	Developing the Framework for a Comprehensive and Evidence Based ACTTION-APS-AAPM Pain Taxonomy (AAAPT) for Acute Pain. The ACTTION (Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks) public-private partnership with the FDA, the American Pain Society, and the American Academy of Pain Medicine are collaborating on the development of an acute pain taxonomy with diagnostic criteria for the major acute pain conditions.	Invited talk
2017	The National Academies of Sciences, Engineering, and Medicine (NASEM) Committee on Pain Management and Regulatory Strategies to Address Prescription Opioid Abuse Consensus Report Out “Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use” (July)	Invited Committee Member / Report Out Panel Member
2017	AAAPT Meeting. Sponsored by the ACTTION (Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks), the American Academy of Pain Medicine (AAPM), and the American Pain Society (APS). (November 3-4)	Invited talk

INVITED PRESENTATIONS - REGIONAL AND OTHER INVITED PRESENTATIONS

1996	UCSF Department of Anesthesia and Perioperative Care, The Changing Practice of Anesthesia Conference, Pain Management/Regional Anesthesia: San Francisco, California, September	Invited talk
1997	UCSF School of Medicine, Pain Research Group: San Francisco, California	Research seminar
1997	UCSF School of Medicine, Department of Anesthesia and Perioperative Care: San Francisco, California	Research seminar
1997	UCSF Department of Pharmacology, Graduate Program in Biomedical Sciences: San Diego, California, December	Invited talk
1998	UCI Department of Microbiology and Molecular Genetics, College of Medicine: Irvine, California, May	Invited talk
1998	UCSF School of Medicine, Department of Anesthesia and Perioperative Care: San Francisco, California	Research seminar
1999	UCSF School of Medicine, Department of Anesthesia and Perioperative Care: San Francisco, California, January	Research seminar

1999	UCSF School of Medicine, Pain Research Group: San Francisco, California, February	Invited talk
2000	UCSF School of Medicine, Department of Anesthesia and Perioperative Care: San Francisco, California, February	Research seminar
2000	UCSF School of Medicine, Pain Research Group: San Francisco, California	Invited talk
2001	UCSF Department of Anesthesia and Perioperative Care, The Changing Practice of Anesthesia Conference, Pain Management/Regional Anesthesia: San Francisco, California, September	Invited talk
2004	UCSF School of Medicine, Department of Medicine, Grand Rounds: San Francisco, California, October	Invited talk
2005	UCSF School of Medicine, Pain Research Group: San Francisco, California, February	Invited talk
2007	UCSD Pain Group: San Diego, California	Invited talk
2007	UCSF Center for Cerebrovascular Research Seminar, June 12	Invited talk
2008	UCSF School of Medicine, Pain Research Group: San Francisco, California, May	Invited talk
2008	Anesiva: South San Francisco, California, July	Invited talk
2008	UCSD Pain Group: San Diego, California	Invited talk
2008	UCSF School of Medicine, Department of Anesthesia and Perioperative Care, Grand Rounds: San Francisco, California	Research presentation
2009	UCSF School of Medicine, Department of Anesthesia and Perioperative Care, Grand Rounds: San Francisco, California	Research presentation
2009	UCSF Department of Anesthesia and Perioperative Care, The Changing Practice of Anesthesia Conference: San Francisco, California, September	Invited talk
2009	UCSF Department of Medicine, Palliative Care Pain Lectures: San Francisco, California, October	Invited talk
2010	Venture Inovation Program (Q83) Forum on Drug Delivery: UCSF Mission Bay Campus, San Francisco, California, March	Invited talk
2010	UCSF Department of Medicine, Palliative Care Fellows Lecture: San Francisco, California	Invited talk

2011	UCSF Pain Summit 2011, May	Course Co-Chair, Moderator, Speaker
2011	UCSF Departments of Anesthesia and Surgery, Joint Ventures in Clinical Excellence: San Francisco, California	Invited talk
2011	UCSF Department of Anesthesia and Perioperative Care, The Changing Practice of Anesthesia Conference: San Francisco, California, September	Invited talk
2011	University of California, San Diego: San Diego, California, December	Invited talk
2011	UCSF School of Medicine, Department of Anesthesia and Perioperative Care, Grand Rounds: San Francisco, California, December	Invited moderator, talk
2011	University of California, San Francisco, Patient Quality and Safety Retreat: San Francisco, California, December	Invited talk
2012	UCSF Departments of Anesthesia and Perioperative Care, Surgery and Medicine (Division of Hospital Medicine), Joint Grand Rounds, Perioperative Medicine: San Francisco, California, April	Moderator
2012	Western Anesthesia Residents' Conference (WARC): Los Angeles, California, May (Does the Capsaicin Receptor Splice Variant TRPV1var Block Activation of Sensory Neurons to Capsaicin?)	Invited talk (mentored)
2012	UCSF Department of Anesthesia and Perioperative Care, The Changing Practice of Anesthesia Conference: San Francisco, California, September (Perioperative Management of the Opioid Tolerant Patient)	Invited talk
2013	UCSF Pain Summit 2013, May	Course Chair, Moderator, Speaker
2013	Western Anesthesia Residents' Conference (WARC): Albuquerque, New Mexico, May (Determining a nociceptive transcriptome by “Deep Sequencing” (RNA-Seq) analysis of sensory ganglia from Sp4 +/- heterozygote mice)	Invited talk (mentored)
2013	UCSF Department of Anesthesia and Perioperative Care, Pain Medicine Grand Rounds, November	Moderator
2014	UCSF Department of Anesthesia and Perioperative Care, The Changing Practice of Anesthesia Conference: San Francisco, California, September (Securing Hospital Approval for Ketamine Use on the Wards)	Invited talk

2014	Western Anesthesia Residents' Conference (WARC): Los Angeles, California, May (Benefits Beyond Pain Control: Multimodal Analgesia Associated with Reduced Hospital Length of Stay)	Invited talk (mentored)
2015	UCSF Department of Anesthesia and Perioperative Care, Pain Medicine Grand Rounds, February	Moderator
2015	UCSF Pain Research Group Lecture, February (Chronification of Pain: The Role of Sp1-like Transcription Factors)	Invited talk
2015	Pain Fellows Lecture (Bench to Bedside)	Invited talk
2015	UCSF Pain Summit, May	Course Chair, Moderator, Speaker
2016	UCSF Department of Surgery Grand Rounds (The Surgeon's Role in Prescribing Narcotics and the Management of Chronic Pain)	Invited talk
2017	Opioid Prescribing Practices Special Grand Rounds (April 19)	Invited talk
2017	UCSF Department of Anesthesia and Perioperative Care Grand Rounds: Pain	Moderator
2017	Napa Pain Conference. (August 18-20) NASEM Presentation: Pain Management and the Opioid Epidemic - Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use.	Invited talk
2017	California Society of Interventional Pain Physicians (CASIPP) 8th Annual Meeting. NASEM Presentation: Pain Management and the Opioid Epidemic - Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use. (September 15-17)	Invited talk
2018	Napa Pain Conference. (August 16-19)	Invited Panel Talk

GOVERNMENT AND OTHER PROFESSIONAL SERVICE

2002 - 2002	BioStar University of California (1)	Grant Review: Ad Hoc
2003 - 2004	National Science Foundation (2)	Grant Review: Ad Hoc
2009 - 2009	National Institute of Health (4)	Grant Review RFA Panel 23
2012 - 2013	Defense Medical Research and Development Program (DMRDP), Department of Defense (DOD)	Grant Reviewer and Member

2016 - 2018	National Academies of Sciences, Engineering, and Medicine, Committee on Pain Management and Regulatory Strategies to Address Prescription Opioid Abuse *Consensus Report, Published July 2017: Pain Management and the Opioid Epidemic - Balancing Societal and Individual Benefits and Risks of Prescription Opioid Abuse" *July 12, 2017: Briefing with the FDA *July 12, 2017: Briefing with the staff of House Energy and Commerce Committee, Subcommittee on Health *July 13, 2017: Consensus Report Public Release Webinar	Member

UNIVERSITY AND PUBLIC SERVICE

SERVICE ACTIVITIES SUMMARY

Division of Pain Medicine: Beginning in 2010, I undertook the formation of a Division of Pain Medicine (pain.ucsf.edu).

UCSF Health: Through my contributions on the interdisciplinary Pain Committee and the Pharmacy and Therapeutics (P&T) Committee, I have provided content expertise and leadership on a wide range of analgesic practice and policy concerns. This includes in depth contributions of a special medical staff committee on opioid prescribing practices that resulted in policy changes, a report out at the level of the Chancellor and presenting at a special Grand Rounds for all medical staff on opioid prescribing practices.

National: I served on the National Academies of Sciences, Engineering, and Medicine, Committee on Pain Management and Regulatory Strategies to Address Prescription Opioid Abuse and authored several key chapters in our Consensus Report, Published July 2017: "Pain Management and the Opioid Epidemic - Balancing Societal and Individual Benefits and Risks of Prescription Opioid Abuse." I was one of four members selected by the chair of the NASEM committee to participate in dissemination of the report by webinar; to FDA leadership and congressional staff committees as well as a number of media outlets.

UCSF CAMPUSWIDE

1997 - 1997	USP Drug Information Writing Contest	Judge
1998 - 1998	Office of the Vice Chancellor, Ad Hoc Committee for Appraisal of Achievement and Promise	Chair
2006 - 2006	Office of the Vice Chancellor, Ad Hoc Committee for Appraisal of Achievement and Promise	Member
2012 - present	Pharmacy and Therapeutics Committee	Member
2015 - 2015	Stewardship Review, Department Chair, UCSF Office of the Vice Provost	Member
2016 - 2016	Ad-hoc Committee, UCSF Medical Staff Services. Faculty professionalism, review of opioid prescribing practices.	Member
2018 - present	UCSF Opioid Task Force	Member

SCHOOL OF MEDICINE

2009 - present	Pathway to Medical Center Discovery in Molecular Medicine	Faculty Member
2010 - 2010	President of Medical Staff - Ad Hoc Committee: Faculty Professionalism	Member
2010 - 2015	Pain Management Services UCSF Medical Center	Medical Director
2010 - 2015	Pain Management Committee	Chair
2010 - 2013	Continuous Pulse Oximetry Project-12L	Physician Champion
2010 - 2013	PCA Ad Hoc Safety Committee	Physician Champion
2010 - 2013	Remote Centralized Monitoring committee	Member
2011 - 2011	UCSF Pain Summit, May 2011	Co-Director
2013 - 2015	UCSF Pain Summits, May 2013 & May 2015	Director
2018 - 2018	Interviewed for Episode 13 of "The Spark: Medical Education for Curious Minds." https://soundcloud.com/the-spark-for-medical-education/the-spark-episode-13-treatment-of-chronic-pain	Interviewee

DEPARTMENTAL SERVICE

1998 - 1998	UCSF Department of Anesthesia and Perioperative Care	Review and Promotions Committee
1999 - 1999	UCSF Department of Anesthesia and Perioperative Care	Junior Faculty Meetings, Junior Faculty Coordinator
2001 - 2001	UCSF Department of Anesthesia and Perioperative Care	Review and Promotions Committee
2006 - 2015	UCSF Department of Anesthesia and Perioperative Care	Scientific Merit Review Committee
2009 - 2009	UCSF Department of Anesthesia and Perioperative Care	Patient Clinical Study Oversight Committee, Ad Hoc Member

2010 - 2015	UCSF Department of Anesthesia and Perioperative Care	Director of Acute Pain Service, Moffitt/Long Hospital
2010 - present	UCSF Department of Anesthesia and Perioperative Care	Chief, Division of Pain Medicine

COMMUNITY AND PUBLIC SERVICE

1995 - 2005	United States Pharmacopeia - USP (Elected Position)	Anesthesiology Expert Advisory Panel Member: (Reviewed and critiqued anesthesia and pain management drug and therapeutic information Published as USP DI. Active for 10 years
2004 - present	Faculty of 1000 Medicine - Anesthesiology & Pain Management (Appointed)	North American Section Head, Pain-Basic Science: Oversight, faculty selection and review of high-impact research summaries
2007 - 2007	Redwood High School: Larkspur, California	Science Fair Judge
2010 - 2017	Gnu Foundation, Kenya	Physician Champion: Linking UCSF to Kilimambogo Mission Hospital, Kenya
2018 - 2018	SF City Impact - Health and Wellness Center. Volunteer physician and health educator for economically disadvantaged patient population in the SF City Impact Health and Wellness Center located in the Tenderloin neighborhood.	Volunteer physician

Prepared: February 22, 2019

RESEARCH AND CREATIVE ACTIVITIES

RESEARCH AND CREATIVE ACTIVITIES SUMMARY

Chemotherapy Induced Peripheral Neuropathy (CIPN): Successful treatment of patients suffering from a wide range of cancers often require the administration of chemotherapeutic agents that are associated with the development of acute and chronic painful conditions. Often referred to as, Chemotherapy Induced Peripheral Neuropathy, CIPN encompasses a wide range of clinical symptoms and pathophysiologic states. The pain associated with platinum-based anticancer agents, is perhaps one of the most recognized and well-studied but also resistant to effective treatments. In fact, no effective therapies exist to prevent or reverse the pain that can limit life-saving anticancer treatments or that degrades the quality of life of cancer survivors. In collaboration with Drs. Miaskowski and Levine, our laboratory is advancing study of non-opioid strategies to block / reverse painful CIPN. I am also collaborating on clinical studies focused on phenotyping and genomic biomarkers of CIPN.

Endovanilloid / Endocannabinoids and TRPV1: In collaboration with Dr. Judith Hellman, in collaboration to identify and further characterize the effects of the endovanilloid / endocannabinoid, N-arachidonoyl dopamine (NADA) and the minor cannabinoids activation of TRPV1 under conditions of tissue injury and sepsis.

Nociceptive Gene Regulation: Identification of receptors / ion channels that respond to noxious stimuli has been at the forefront of a new understanding of peripheral pain transduction. A seminal finding was the isolation of the capsaicin receptor (also known as VR1 and now termed TRPV1) that is essential for inflammatory pain and hyperalgesia. Having played a critical role in the initial isolation and characterization of TRPV1 (Nature ’97), my laboratory has been pioneering a new understanding of the transcriptional regulation of nociceptive genes. More specifically, how inflammation and nerve injury drive persistent pain states (Acute to Chronic) through the expression of TRPV1 and other nociceptive channels.

RESEARCH AWARDS - CURRENT

1. T32 GM08440	Faculty, Mentor; Pain and Addiction Program Administrator		Judith Hellman (PI)
NIH		06/2017	present
Basic Science Anesthesia Research Training Grant			
Provide oversight and research training opportunities in the area of peripheral pain transduction. Active Fellow: Man-Cheung Lee			
2.	Principal Investigator		Schumacher (PI)
UCSF Department of Anesthesia and Perioperative Care		07/01/2018	06/30/2019
Anesthesia Department Research Support Award (Mechanisms and Blockade of Platinum-based Painful Neuropathy)		$ 80,000 direct/yr 1	$ 80,000 total

Prepared: February 22, 2019

RESEARCH AWARDS - Pending

1. P01 CA233703 Co-Investigator Miaskowski, Levine (PI)

NIH/NCI (Pending)

Chronic Neurotoxicity Associated With Chemotherapy: Risk Factors and Mechanisms — $ 5,128,982 direct/yr 1

The major goals of this project are to: 1) determine the relationships between chronic CIPN and audiovestibular neurotoxicity associated with platinum and taxane CTX; 2) identify common and distinct phenotypic and genomic risk factors for chronic CIPN and audiovestibular neurotoxicity; 3) determine the relationships between stress and chronic CIPN and audiovestibular neurotoxicity; 4) determine the impact of chronic CIPN and audiovestibular neurotoxicity on important patient outcomes (e.g., falls, symptoms, QOL); and 5) use preclinical models to evaluate the role of nociceptor neuroplasticity and the impact of stress on the development of chronic CIPN.

RESEARCH AWARDS - PAST

1. Principal Investigator Schumacher (PI)

UCSF Research Evaluation UCSF Research Evaluation	1997	1999
Characterization of NGF Regulated Proteins Expressed by Primary Sensory Neurons	$ 15,000 direct/yr 1	$ 15,000 total

2. Principal Investigator Schumacher (PI)

Radiometer / John W. Severinghaus Fellow in Anesthesia Research - UCSF	1997	1999
Molecular Mechanisms of Nerve Growth Factor (NGF) Mediated Hyperalgesia and Pain	$ 50,000 direct/yr 1	$ 100,000 total

3. R01 NS38737 Principal Investigator Scumacher (PI)

NIH R01 NIH/NINDS	1997	2007
Capsaicin Receptor Subtypes in Pain Transduction (*No-cost extension 2006-2007)	$ 101,234 direct/yr 1	$ 1,079,702 total

4. Principal Investigator Schumacher (PI)

	Foundation for Anesthesia Education Research New Investigator Award	1998	2000
	The Role of Capsaicin Receptors in Nociception	$ 70,000 direct/yr 1	$ 140,000 total
5.	Principal Investigator		Schumacher (PI)
	UCSF E. Ackerman Foundation for Research in Medicine	2001	2003
	Shared Equipment AProposal: Cryostat	$ 15000 direct/yr 1	$ 15000 total
6.	Principal Investigator		Schumacher (PI)
	Frontiers in Anesthesia Research Award International Anesthesia Research Society (IARS)	2001	2006
	Stretch-Inactivated Channels in Pain Transduction	$ 100,000 direct/yr 1	$ 500,000 total
7.	T32 - PACCTR Co-Mentor		
	NIH (UCSF)	2006	2007
	Pathways to Careers in Clinical and Translational Research	$ Fellow's salary direct/yr 1	
8.	Principal Investigator		Schumacher (PI)
	UCSF Springer H. Mem. Foundation	2007	2008
	REAC Hardship	$ 25,000 direct/yr 1	$ 25,000 total
9.	Mentor		
	Foundation for Anesthesia Education and Research	2008	2008
	Medical Student Anesthesia Research Fellowship	$ student stipend direct/yr 1	

10.	Principal Investigator		Schumacher (PI)
	National Headache Foundation Research Grant	2008	2009
	Regulation of capsaicin receptor (TRPV1) expression in meningeal sensory neurons under inflammatory conditions.	$ 16,000 direct/yr 1	$ 16,000 total
11.	Principal Investigator		Schumacher (PI)
	UCSF / SOM Bridge Funding Grant	2008	2009
	Capsaicin Receptor Subtypes in Pain Transduction	$ 73,750 direct/yr 1	$ 73,750 total
12.	R01DK046285-09 Co-Investigator		
	NIH	2008	2013
	Neural Regulation of Pancreatitis	$ 250,000 direct/yr 1	
13.	R01 NS38737-08 Principal Investigator		
	NIH	2009	2013
	Capsaicin Receptor subtypes in Pain Transduction	$ 218,750 direct/yr 1	$ 1,120,481 total
14.	3R01NS038737-09S1 Principle Investigator		Schumacher (PI)
	NIH	2010	2010
	Supplement: Optogenetics and TRPV1	$ 77,250 direct/yr 1	$ 77,250 total
15.	Principal Investigator		Schumacher (PI)
	Office of Naval Research/UCSD	2010	2011
	Pain Management by an Endogenous Antihyperalgesic	$ 88,186 direct/yr 1	$ 88,186 total

16. T32 GM08440 — Co Investigator — Young (PI)
Basic Science Anesthesia Research Training Grant — 2011 — 2016

17. N/A — Principal Investigator / Program Manager
NIH / NIDA — 07/10/2012 — 09/30/2013
UCSF Center of Excellence in Pain Education — $ 98,647 direct/yr 1 — $ 98,647 total

18. — Principal Investigator
UCSF Department of Anesthesia and Perioperative Care — 04/01/2013 — 06/30/2013
Anesthesia Department Research Support Award Bridge Funding — $ 25,000 direct/yr 1

19. — Principal Investigator
UCSF Department of Anesthesia and Perioperative Care — 11/12/2014 — 06/30/2015
Anesthesia Department Research Support Award Bridge Funding — $ 59,490 direct/yr 1

20. IRB Number: 13-12177 — Principal Investigator
05/01/2015 — 04/30/2016
Clinical Investigation. Study Title: Effect of a multimodal analgesic protocol on post-operative pain, opioid consumption and readiness for discharge in adult patients undergoing primary knee or hip replacement.

21. — Principal Investigator
UCSF Department of Anesthesia and Perioperative Care — 07/01/2015 — 06/30/2016
Anesthesia Department Research Support Award Bridge Funding (Transcriptional Mechanisms and Blockade of Platinum Based Painful Neuropathy) — $ 80,000 direct/yr 1

22.	Contract Number: HHSN271201500052C	Principal Investigator/Project Manager		Schumacher (PI)
	NIH / NIDA		07/15/2015	07/14/2016
	NIH Pain Consortium Centers of Excellence in Pain Education		$ 77,867 direct/yr 1	$ 77,867 total
23.		Principal Investigator		Schumacher (PI)
	UCSF Department of Anesthesia and Perioperative Care		01/01/2016	06/30/2017
	Anesthesia Department Research Support Award		$ 80,000 direct/yr 1	$ 80,000 total
24.				Schumacher (PI)
			07/01/2017	06/30/2018
	Anesthesia Department Research Support Award			$ 44,436 total
25.	T32 GM08440	Faculty, Mentor; Pain and Addiction Program Administrator		Judith Hellman (PI)
	NIH		7/2012	6/2017
	Provide oversight and research training opportunities in the area of peripheral pain transduction.			
26.		Principal Investigator		Schumacher (PI)
	UCSF Department of Anesthesia and Perioperative Care		07/01/2017	06/30/2018
	Research Award (Transcriptional Mechanisms and Blockade of Platinum-based Painful Neuropathy)		$ 80,000 direct/yr 1	$ 80,000 total
27.		Principal Investigator		Schumacher (PI)
	UCSF Department of Anesthesia and Perioperative Care		07/01/2017	06/30/2018
	Supplemental Research Award (Transcriptional Mechanisms and Blockade of Platinum-based Painful Neuropathy)		$ 43,436 direct/yr 1	$ 43,436 total

PEER REVIEWED PUBLICATIONS

1. **Schumacher MA**, Alksne JF. Mechanisms of whole blood-induced cerebral arterial contraction. *Neurosurgery*.1981 Sep;9(3):275-82.
2. Leffert H, Schenk D, Hubert J, Skelley H, **Schumacher M**, Ariyasu R, Ellisman M, Koch K, and Keller G. Hepatic (Na+,K+)-ATPase: a current view of its structure, function and localization in rat liver as revealed by studies with monoclonal antibodies. *Hepatology*.1985 May-Jun;5(3):501-7.
3. **Schumacher M**, Camp S, Maulet Y, Newton M, MacPhee-Quigley K, Taylor S, Friedmann T, Taylor P. Primary structure of Torpedo californica acetylcholinesterase deduced from its cDNA sequence. *Nature*.1986 Jan 30-Feb 5;319(6052):407-9.
4. Taylor P, **Schumacher M**, Maulet Y, Newton M. A molecular perspective on the polymorphism of acetylcholinesterase. *Trends Pharmacol Sci*.1986 Jan 01.Volume 7, 321-323. doi:10.1016/0165-6147(86)90370-6.
5. **Schumacher M**, Camp, S, Maulet Y, Newton M, MacPhee-Quigley K, Taylor S, Friedmann T, and Taylor P. Primary structure of acetylcholinesterase - Implications for regulation and function. *Federation Proceedings*. 45: 2976-2980, 1986.
6. Taylor P, **Schumacher M**, MacPhee-Quigley K, Friedmann T, and Taylor S. The structure of acetylcholinesterase - relationship to its function and cellular disposition. *Trends Neurosci*. 10: 93-96, 1987.
7. **Schumacher M**, Maulet Y, Camp S, and Taylor P. Multiple messenger RNA species give rise to the structural diversity in acetylcholinesterase. *J Biol Chem*. 1988 Dec 15;263(35):18979-87.
8. Brake A, **Schumacher M**, Julius D. ATP receptors in sickness, pain and death. *Chem Biol*. 1996 Apr;3(4):229-32.
9. Caterina MJ, **Schumacher MA**, Tominaga M, Rosen TA, Levine JD, and Julius D. The Capsacin Receptor: A Heat-Activated Ion Channel in the Pain Pathway. *Nature* 1997 389: 816-824.
10. **Schumacher MA**, Moff I, Sudanagunta SP, Levine JD. Molecular cloning of an N-terminal splice variant of the capsaicin receptor. Loss of N-terminal domain suggests functional divergence among capsaicin receptor subtypes. *J Biol Chem*. 2000 Jan 28;275(4):2756-62.
11. **Schumacher MA**, Jong BE, Frey SL, Sudanagunta SP, Capra NF, Levine JD. The stretch-inactivated channel, a vanilloid receptor variant, is expressed in small-diameter sensory neurons in the rat. *Neurosci Lett*. 2000 Jun 30;287(3):215-8.
12. Eilers H, Philip LA, Bickler PE, McKay WR, **Schumacher MA**. The reversal of fentanyl-induced tolerance by administration of "small-dose" ketamine. *Anesth Analg*. 2001 Jul;93(1):213-4.
13. Xue Q, Yu Y, Trilk SL, Jong BE, **Schumacher MA**. The genomic organization of the gene encoding the vanilloid receptor: evidence for multiple splice variants. *Genomics*. 2001 Aug;76(1-3):14-20.

14. Ständer S, Moormann C, **Schumacher M**, Buddenkotte J, Artuc M, Shpacovitch V, Brzoska T, Lippert U, Henz BM, Luger TA, Metze D, Steinhoff M. Expression of vanilloid receptor subtype 1 in cutaneous sensory nerve fibers, mast cells, and epithelial cells of appendage structures. *Exp Dermatol*. 2004 Mar;13(3):129-39.

15. Eilers H, **Schumacher MA**. Opioid-induced respiratory depression: are 5-HT4a receptor agonists the cure? *Mol Interv*. 2004 Aug;4(4):197-9.

16. Eilers H, Trilk SL, Lee SY, Xue Q, Jong BE, Moff I, Levine JD, **Schumacher MA**. Isolation of an mRNA binding protein homologue that is expressed in nociceptors. *Eur J Neurosci*. 2004 Nov;20(9):2283-93.

17. Xue Q, Jong B, Chen T, **Schumacher MA**. Transcription of rat TRPV1 utilizes a dual promoter system that is positively regulated by nerve growth factor. *J Neurochem*. 2007 Apr;101(1):212-22.

18. Eilers H, Lee SY, Hau CW, Logvinova A, **Schumacher MA**. The rat vanilloid receptor splice variant VR.5'sv blocks TRPV1 activation. *Neuroreport*. 2007 Jul 2;18(10):969-73.

19. Andres-Enguix I, Caley A, Yustos R, **Schumacher MA**, Spanu PD, Dickinson R, Maze M, Franks NP. Determinants of the anesthetic sensitivity of two-pore domain acid-sensitive potassium channels: molecular cloning of an anesthetic-activated potassium channel from Lymnaea stagnalis. *J Biol Chem*. 2007 Jul 20;282(29):20977-90.

20. Zecharia AY, Nelson LE, Gent TC, **Schumacher M**, Jurd R, Rudolph U, Brickley SG, Maze M, Franks NP. The involvement of hypothalamic sleep pathways in general anesthesia: testing the hypothesis using the GABAA receptor beta3N265M knock-in mouse. J *Neurosci*. 2009 Feb 18;29(7):2177-87.

21. **Schumacher MA**, Eilers H. TRPV1 splice variants: structure and function. *Front Biosci* (Landmark Ed). 2010 Jun 1;15:872-82.

22. **Schumacher MA**. Transient receptor potential channels in pain and inflammation: therapeutic opportunities. *Pain Pract*. 2010 May-Jun;10(3):185-200.

23. Eilers H, Cattaruzza F, Nassini R, Materazzi S, Andre E, Chu C, Cottrell GS, **Schumacher M**, Geppetti P, Bunnett NW. Pungent general anesthetics activate transient receptor potential-A1 to produce hyperalgesia and neurogenic bronchoconstriction. *Anesthesiology*. 2010 Jun;112(6):1452-63.

24. Turnbull JH, Gebauer SL, Miller BL, Barbaro NM, Blanc PD, **Schumacher MA**. Cutaneous nerve transection for the management of intractable upper extremity pain caused by invasive squamous cell carcinoma. *J Pain Symptom Manage*. 2011 Jul;42(1):126-33.

25. Chu C, Zavala K, Fahimi A, Lee J, Xue Q, Eilers H, **Schumacher MA**. Transcription factors Sp1 and Sp4 regulate TRPV1 gene expression in rat sensory neurons. *Mol Pain*. 2011 Jun 6;7:44. (Accessed 7668 times as of July 2015.)

26. **Schumacher MA**. Pain Management for the Obese Sleep Apnea Patient: Insights for ICU Practitioners. *ICU Director*. 2012;3:80-84.

27. **Schumacher MA**. Back Pain and the Mineralocorticoid Receptor: Is There a Connection? *Anesthesiology*. 2012 Nov;117(5):951-2.

28. Wilhelmsen K, Khakpour S, Tran A, Sheehan K, **Schumacher M**, Xu F, Hellman J. The Endocannabinoid/Endovanilloid N-Arachidonoyl Dopamine (NADA) and Synthetic

Cannabinoid WIN55,212-2 Abate the Inflammatory Activation of Human Endothelial Cells. *J Biol Chem*. 2014 May 9;289(19):13079-100.

29. Zavala K, Lee J, Chong J, Sharma M, Eilers H, **Schumacher MA**. The anticancer antibiotic mithramycin-A inhibits TRPV1 expression in dorsal root ganglion neurons. *Neurosci Lett*. 2014 Aug 22;578:211-6.

30. **Schumacher M**, Pasvankas G. Topical capsaicin formulations in the management of neuropathic pain. *Prog Drug Res*. 2014;68:105-28.

31. Guan Z, Hellman J and **Schumacher M**. Contemporary views on inflammatory pain mechanisms: TRPing over innate and microglial pathways. *F1000Res*. 2016 Sep 30;5. pii: F1000 Faculty Rev-2425. eCollection 2016.

32. Miaskowski C, Mastick J, Paul SM, Topp K, Smoot B, Abrams G, Chen LM, Kober KM, Conley YP, Chesney M, Bolla K, Mausisa G, Mazor M, Wong M, **Schumacher M**, Levine JD. Chemotherapy-Induced Neuropathy in Cancer Survivors. *J Pain Symptom Manage*. 2017 Aug;54(2):204-218.e2. doi: 10.1016/j.jpainsymman.2016.12.342. Epub 2017 Jan 4.

33. Lawton SK, Xu F, Tran A, Wong E, Prakash A, **Schumacher M**, Hellman J, Wilhelmsen K. N-Arachidonoyl Dopamine Modulates Acute Systemic Inflammation via Nonhematopoietic TRPV1. *J Immunol*. 2017 Aug 15;199(4):1465-1475. doi: 10.4049/jimmunol.1602151. Epub 2017 Jul 12.

34. Clark DJ, **Schumacher M**. America's Opioid Epidemic: Supply and Demand Considerations. *Anesth Analg*. 2017 Nov;125(5):1667-1674.

35. Kent ML, Tighe PJ, Belfer I, Brennan TJ, Bruehl S, Brummett CM, Buckenmaier CC 3rd, Buvanendran A, Cohen RI, Desjardins P, Edwards D, Fillingim R, Gewandter J, Gordon DB, Hurley RW, Kehlet H, Loeser JD, Mackey S, McLean SA, Polomano R, Rahman S, Raja S, Rowbotham M, Suresh S, Schachtel B, Schreiber K, **Schumacher M**, Stacey B, Stanos S, Todd K, Turk DC, Weisman SJ, Wu C, Carr DB, Dworkin RH, Terman G. The ACTTION-APS-AAPM Pain Taxonomy (AAAPT) Multidimensional Approach to Classifying Acute Pain Conditions. *J Pain*. 2017 May;18(5):479-489.

36. Kent ML, Tighe PJ, Belfer I, Brennan TJ, Bruehl S, Brummett CM, Buckenmaier CC 3rd, Buvanendran A, Cohen RI, Desjardins P, Edwards D, Fillingim R, Gewandter J, Gordon DB, Hurley RW, Kehlet H, Loeser JD, Mackey S, McLean SA, Polomano R, Rahman S, Raja S, Rowbotham M, Suresh S, Schachtel B, Schreiber K, Schumacher M, Stacey B, Stanos S, Todd K, Turk DC, Weisman SJ, Wu C, Carr DB, Dworkin RH, Terman G. The ACTTION-APS-AAPM Pain Taxonomy (AAAPT) Multidimensional Approach to Classifying Acute Pain Conditions. *Pain Med*. 2017 May 1;18(5):947-958. doi: 10.1093/pm/pnx019.

37. Miaskowski C, Mastick J, Paul SM, Abrams G, Cheung S, Sabes JH, Kober KM, **Schumacher M**, Conley YP, Topp K, Smoot B, Mausisa G, Mazor M, Wallhagen M, Levine JD. Impact of chemotherapy-induced neurotoxicities on adult cancer survivors' symptom burden and quality of life. *J Cancer Surviv*. 2018 Apr;12(2):234-245. doi: 10.1007/s11764-017-0662-8. Epub 2017 Nov 20.

38. Miaskowski C, Paul SM, Mastick J, **Schumacher M**, Conley YP, Smoot B, Abrams G, Kober KM, Cheung S, Henderson-Sabes J, Chesney M, Mazor M, Wallhagen M, Levine JD. Hearing loss and tinnitus in survivors with chemotherapy-induced neuropathy. *Eur J Oncol Nurs*. 2018 Feb;32:1-11. doi: 10.1016/j.ejon.2017.10.006. Epub 2017 Nov 7.

39. Kober KM, Olshen A, Conley YP, **Schumacher M**, Topp K, Smoot B, Mazor M, Chesney M, Hammer M, Paul SM, Levine JD, Miaskowski C. Expression of mitochondrial dysfunction-related genes and pathways in paclitaxel-induced peripheral neuropathy in breast cancer survivors. *Mol Pain*. 2018 Jan-Dec;14:1744806918816462. doi: 10.1177/1744806918816462. Epub 2018 Nov 14.

40. Miaskowski C, Paul SM, Mastick J, Abrams G, Topp K, Smoot B, Kober KM, Chesney M, Mazor M, Mausisa G, **Schumacher M**, Conley YP, Sabes JH, Cheung S, Wallhagen M, Levine JD. Associations Between Perceived Stress and Chemotherapy-Induced Peripheral Neuropathy and Otoxicity in Adult Cancer Survivors. *J Pain Symptom Manage*. 2018 Jul;56(1):88-97. doi: 10.1016/j.jpainsymman.2018.02.021. Epub 2018 Mar 7.

41. Peniche A, Poree L, **Schumacher M**, Yu X. Integrating Patient-Controlled Analgesia Using Implanted Intrathecal Pumps for Postoperative Pain Management: A Case Report. *A A Pract*. 2018 Jun 1;10(11):285-287.

42. Kober K, Olshen A, Conley YP, **Schumacher M,** Topp K, Smoot B, Mazor M, Chesney M, Hammer M, Paul SM, Levine JD, Miaskowski C. Expression of mitochondrial dysfunction-related genes and pathways in paclitaxel-induced peripheral neuropathy in breast cancer survivors. Mol Pain. 2018 Jan-Dec;14:1744806918816462. doi: 10.1177/1744806918816462. Epub 2018 Nov 14.

43. Kober KM, Mazor M, Abrams G, Olshen A, Conley YP, Hammer M, **Schumacher M**, Chesney M, Smoot B, Mastick J, Paul SM, Levine JD, Miaskowski C. Phenotypic Characterization of Paclitaxel-Induced Peripheral Neuropathy in Cancer Survivors. *J Pain Symptom Manage*. 2018 Dec;56(6):908-919.e3. doi: 10.1016/j.jpainsymman.2018.08.017. Epub 2018 Aug 30.

44. Miaskowski C, Paul SM, Mastick J, Abrams G, Topp K, Smoot B, Kober KM, Chesney M, **Schumacher M**, Conley YP, Hammer M, Cheung S, Borsook D, Levine JD. Contribution of Loss of Large Fiber Function to Pain in 2 Samples of Oncology Patients. *Clin J Pain*. 2019 Jan;35(1):37-42. doi: 10.1097/AJP.0000000000000649.

45. Wong ML, Cooper BA, Paul SM, Abrams G, Topp K, Kober KM, Chesney MA, Mazor M, **Schumacher MA**, Conley YP, Levine JD, Miaskowski C. Age-related differences in patient-reported and objective measures of chemotherapy-induced peripheral neuropathy among cancer survivors. *Support Care Cancer*. 2019 Feb 15. doi: 10.1007/s00520-019-04695-3. [Epub ahead of print]

46. Sheehan K, Lee J, Chong J, Zavala K, Sharma M, Philipsen S, Maruyama T, Xu Z, Guan Z, Eilers H, Kawamata T, **Schumacher M**. Transcription factor Sp4 is required for hyperalgesic state persistence. *PLOS One*. In press.

REVIEW ARTICLES

1. Eilers H, **Schumacher MA**. Mechanosensitivity of Primary Afferent Nociceptors in the Pain Pathway. In: Kamkin A, Kiseleva I, eds. Mechanosensitivity in Cells and Tissues. Academia Moscow; 2005.

2. **Schumacher M**, Xue Q. New insights into the role of the capsaicin receptor (TRPV1) in inflammatory pain. Cell Science 3:1-6, 2007.

3. Pasvankas G, **Schumacher MA**. Pain Management: Total patient care for the treatment of painful conditions. *San Francisco Medicine - Journal of the San Francisco Medical Society* 2010; 83(10):12-13.

4. Naidu R, Shah S, **Schumacher M**. The Prescription Opioid Epidemic: Challenges and Opportunities. *CSA Blog*. September 20, 2016. http://members.csahq.org/blog/2016/09/20/prescription-opioid-epidemic-challenges-and-opportunities-california-pain-physicians
5. De Pinto M, Pasvankas G, Yu X, Poree L, Gritzner S, **Schumacher M**. Pain Management at UCSF. Serving Bay Area Patients. San Francisco Marin Medicine. *Journal of the San Francisco Marin Medical Society*. 2017 June 90(5): 24-25.

BOOKS AND CHAPTERS

1. Taylor P, **Schumacher M**, Gibney G, Maulet Y, and Quigley K. Molecular studies of acetylcholinesterase structure. In: Sellin LC, Libelins R, and Thesleff S, eds. Fernstein Symposium Series, L.C. Vol. 13. Amsterdam: Elsevier; 1989.
2. Way WL, Fields HL, and **Schumacher MA**. Opioid Analgesics and Antagonists. In: Katzung B, ed. Basic and Clinical Pharmacology, 8th Edition. The McGraw-Hill Companies; 2001.
3. **Schumacher MA** and Eilers H. Sensory Processing: Peripheral Nociceptors. In: Evers A, Maze M, eds. Anesthetic Pharmacology: Physiologic Principles and Clinical Practice. A Companion to Miller's Anesthesia. Philadelphia, PA: Churchill Livingston/Elsevier; 2004:173-185.
4. **Schumacher MA**, Basbaum AI, and Way WL. Opioid Analgesics and Antagonists. In: Katzung B, ed. Basic and Clinical Pharmacology, 9th Edition. The McGraw-Hill Companies; 2004.
5. Eilers H, **Schumacher MA**. Mechanosensitivity of Primary Afferent Nociceptors in the Pain Pathway. In: Kamkin A, Kiseleva I, editors. Mechanosensitivity in Cells and Tissues. Moscow: Academia; 2005.
6. **Schumacher MA**, Basbaum AI, and Way WL. Opioid Analgesics and Antagonists. In: Katzung B, ed. Basic and Clinical Pharmacology, 10th Edition. The McGraw-Hill Companies; 2007.
7. **Schumacher MA**, Basbaum AI, and Way WL. Opioid Analgesics and Antagonists. In: Katzung B, ed. Basic and Clinical Pharmacology, 11th Edition. The McGraw-Hill Companies; 2009.
8. **Schumacher MA** and Eilers H. Other Ion-channel and receptor ligands for analgesia. Basic Principles and Clincal Practice. In: Evers A, Maze M, Kharasch E, eds. Anesthetic Pharmacology: 2nd Edition. Cambridge University Press; 2011.
9. **Schumacher MA**, Basbaum AI, and Way WL. Opioid Analgesics & Antagonists. In: Katzung BG, Trevor AJ, Masters SB, eds. Basic and Clinical Pharmacology. 12th ed. McGraw-Hill Education; 2012.
10. **Schumacher MA**, Basbaum AI, and Naidu R. Opioid Analgesics & Antagonists. In: Katzung BG, Trevor AJ, eds. Basic and Clinical Pharmacology. 13th ed. McGraw-Hill Education; 2015.
11. **Schumacher MA** and De Pinto M. Learnings from the Past to Understand Acute and Chronic Pain. In: Friedman H, ed. Encyclopedia of Mental Health, 2nd Edition. Elsevier; 2015.

12. **Schumacher MA**, Basbaum AI, and Naidu R. Chapter 31: Opioid Analgesics & Antagonists. In: Katzung BG, Trevor AJ, eds. Basic and Clinical Pharmacology. 14th ed. McGraw-Hill Education; 2018.
13. **Schumacher M**. Chapter 3. Chapter 5. In Bonnie RJ, Ford MA, Phillips JK, Eds. Pain Management and the Opioid Epidemic. Balancing Societal and Individual Benefits and Risks of Prescription Opioid Abuse. The National Academy of Sciences, Engineering and Medicine. The National Academies Press. Washington, DC. 2017. July.
14. **Schumacher M**, Fukuda K. Chapter 24. Opioids. In: Gropper M, Erikkson L, eds. Miller's Anesthesia, 9th Edition. Elsevier. in press.

PATENTS ISSUED OR PENDING

1. UCSF INVENTION DISCLOSURE Thoracotomy Pain Management Strips UCSF Case # SF2009-015
2. Patent application UCSF-435 WO, "Methods and Composition for the Treatment of Pain"
3. UCSF INVENTION DISCLOSURE: Treatment and Prevention of Chemotherapy-Induced Peripheral Neuropathy (CIPN) and Neuropathic Pain. UCSF Case #2016-083

OTHER CREATIVE ACTIVITIES

1. Division of Pain Medicine Website (http://pain.ucsf.edu/#) Live April 2014
2. Anesthesia Pain Case Presentation: The Opioid Tolerant Patient
3. Anesthesia Resident Board Review handout (17 pages) updated annually. Topic: Pain
4. Anesthesia 110 - Acute and Chronic Pain (slide presentation)
5. 2010 Pain Medicine: UCSF Department of Anesthesia Internet Wiki Page: Content and organization - Board Review Questions - Pain Novel Pharmacotherapy: The old becomes 'new' (slide presentation)
6. NIH Center of Excellence in Pain Education Case Module (Interprofessional Management of Acute to Chronic Leg Pain)
7. NIH Center of Excellence in Pain Education Case Module (Pain Management in an Adult with PTSD and Opioid Use Disorder in the Perioperative Setting)
8. Pain: New Insights and New (and Old) Treatments, "Back to the Future" of Pain Medicine. UC TV. https://www.youtube.com/watch?v=oPRn1Pk5OCo. http://www.uctv.tv.
9. Mark Schumacher interviewed for:
   Cooney, R. All Hands on Deck-Addressing the Nation's Opioid Epidemic. The Lancet United States of Health Blog. July 27, 2017. http://usa.thelancet.com/blog/2017-07-27-all-hands-deck—addressing-nation’s-opioid-epidemic
10. Mark Schumacher interviewed for:
    Healy, M. The U.S. should rethink its entire approach to painkillers and the patients addicted to them, panel urges. Los Angeles Times. July 13, 2017. http://www.latimes.com/science/sciencenow/la-sci-sn-opioid-crisis-recommendations-20170713-story.html

Mark A. Schumacher
University of California, San Francisco
Professor, Dept. of Oral and Maxillofacial Surgery

Prior Testimony

1. Sullivan v. University of California, et al. (Sup. Ct. of CA, Docket CGC02414614)

APPENDIX 2

T. SCHUMACHER - MATERIALS CONSIDERED

1. Aasvang, E. and H. Kehlet (2005). "Surgical management of chronic pain after inguinal hernia repair." Br J Surg. 92(7): 795-801.

2. Abdel Shaheed, C., C. G. Maher, K. A. Williams, R. Day, and A. J. McLachlan. 2016. 'Efficacy,

3. Tolerability, and Dose-Dependent Effects of Opioid Analgesics for Low Back Pain: A Systematic Review and Meta-analysis', JAMA Intern Med, 176: 958-68.

4. Abdulla, F. A. and P. A. Smith (1998). "Axotomy reduces the effect of analgesic opioids yet increases the effect of nociceptin on dorsal root ganglion neurons." J Neurosci 18(23): 9685-9694.

5. Ahern, B. J., et al. (2010). "Pharmacokinetics of fentanyl administered transdermally and intravenously in sheep." Am J Vet Res 71(10): 1127-1132.

6. Alford, D. P., et al. (2016). "SCOPE of Pain: An Evaluation of an Opioid Risk Evaluation and Mitigation Strategy Continuing Education Program." Pain Med 17(1): 52-63.

7. Allen, S. C. (2008). "Neuropathic pain - the case for opioid therapy." Oncology. 74(Suppl 1): 76-82. Epub 2008 Aug 2028.

8. Angst, M. S., and J. D. Clark. 2006. 'Opioid-induced hyperalgesia: a qualitative systematic review', Anesthesiology, 104: 570-87.

9. Anon. Persuading the Prescribers: Pharmaceutical Marketing and its Influence on Physicians and Patients. November 11, 2013. http://www.pewtrusts.org/en/research-and-analysis/fact-sheets/2013/11/11/persuading-the-prescribers-pharmaceutical-industry-marketing-and-its-influence-on-physicians-and-patients

10. Armaghani, S. J., D. S. Lee, J. E. Bible, K. R. Archer, D. N. Shau, H. Kay, C. Zhang, M. J. McGirt, and C. J. Devin. 2014. 'Preoperative opioid use and its association with perioperative opioid demand and postoperative opioid independence in patients undergoing spine surgery', Spine (Phila Pa 1976), 39: E1524-30.

11. Avorn, J., and S. B. Soumerai. 1983. 'Improving drug-therapy decisions through educational outreach. A randomized controlled trial of academically based "detailing"', N Engl J Med, 308: 1457-63.

12. Baker, D. W. 2017. 'History of The Joint Commission's Pain Standards: Lessons for Today's Prescription Opioid Epidemic', JAMA, 317: 1117-18.

13. Baldini, A., M. Von Korff, and E. H. Lin. 2012. 'A Review of Potential Adverse Effects of Long-Term Opioid Therapy: A Practitioner's Guide', Prim Care Companion CNS Disord, 14.

14. Ballantyne, J. C., and N. S. Shin. 2008. 'Efficacy of opioids for chronic pain: a review of the evidence', Clin J Pain, 24: 469-78.

15. Barclay, J. S., J. E. Owens, and L. J. Blackhall. 2014. 'Screening for substance abuse risk in cancer patients using the Opioid Risk Tool and urine drug screen', Support Care Cancer, 22: 1883-8.

16. Barfield, E. and A. Solomon (2013). "An adolescent female with chronic musculoskeletal pain." Clin Pediatr (Phila) 52(7): 684-686.

17. Basbaum, A. I., et al. (2009). "Cellular and molecular mechanisms of pain." Cell 139(2): 267-284.

18. Becker, D. E. 2010. 'Pain management: Part 1: Managing acute and postoperative dental pain', Anesth Prog, 57: 67-78; quiz 79-80.

19. Becker, N., et al., Treatment outcome of chronic non-malignant pain patients managed in a danish multidisciplinary pain centre compared to general practice: a randomised controlled trial. Pain, 2000. 84(2-3): p. 203-11.

20. Bell, R. F. (1999). "Low-dose subcutaneous ketamine infusion and morphine tolerance." Pain. 83(1): 101-103.

21. Bell, R. F. and E. Kalso (2004). "Is intranasal ketamine an appropriate treatment for chronic non-cancer breakthrough pain?" Pain 108(1-2): 1-2.

22. Bell, R. F., et al. (2005). "Peri-operative ketamine for acute post-operative pain: a quantitative and qualitative systematic review (Cochrane review)." Acta Anaesthesiol Scand. 49(10): 1405-1428.

23. Ben-Ari, A., et al. (2007). "Chronic administration of ketamine for analgesia." J Pain Palliat Care Pharmacother. 21(1): 7-14.

24. Benitez-Rosario, M. A., et al. (2004). "Opioid switching from transdermal fentanyl to oral methadone in patients with cancer pain." Cancer. 101(12): 2866-2873.

25. Benitez-Rosario, M. A., et al. (2009). "Morphine-methadone opioid rotation in cancer patients: analysis of dose ratio\ predicting factors." J Pain Symptom Manage. 37(6): 1061-1068. Epub 2009 Jan 1025.

26. Biron, R. T., E. V. Hersh, H. D. Barber, and R. J. Seckinger. 1996. 'A pilot investigation: post-surgical analgesic consumption by dental implant patients', Dentistry, 16: 12-3.

27. Bohnert, A. S., J. E. Logan, D. Ganoczy, and D. Dowell. 2016. 'A Detailed Exploration Into the Association of Prescribed Opioid Dosage and Overdose Deaths Among Patients With Chronic Pain', Med Care, 54: 435-41.

28. Bohnert, A. S., M. Valenstein, M. J. Bair, D. Ganoczy, J. F. McCarthy, M. A. Ilgen, and F. C. Blow. 2011. 'Association between opioid prescribing patterns and opioid overdose-related deaths', JAMA, 305: 1315-21.

29. Bohnert, A.S., et al., "Association between opioid prescribing patterns and opioid overdose-related deaths", 305(13) JAMA 1315, 1321 (2011).

30. Bonica, J. J. 1990. 'Evolution and current status of pain programs', *J Pain Symptom Manage*, 5: 368-74.

31. Bonnie, R. J. (2017). Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use. J. K. Phillips, M. A. Ford and R. J. Bonnie. Washington (DC).

32. Booth, Martin, Opium: A History (St. Martin's Press 1998).

33. Bortolussi, R., et al. (2004). "Opioid consumption in hospitals of the Friuli-Venezia Giulia region: a four-year retrospective study." Tumori 90(1): 96-102.

34. Boscarino, J. A., M. R. Rukstalis, S. N. Hoffman, J. J. Han, P. M. Erlich, S. Ross, G. S. Gerhard, and W. F. Stewart. 2011. 'Prevalence of prescription opioid-use disorder among chronic pain patients: comparison of the DSM-5 vs. DSM-4 diagnostic criteria', J Addict Dis, 30: 185-94.

35. Bostrom, E., M. Hammarlund-Udenaes, and U. S. Simonsson. 2008. 'Blood-brain barrier transport helps to explain discrepancies in in vivo potency between oxycodone and morphine', *Anesthesiology*, 108: 495-505.

36. Brat, G.A., et al., Postsurgical prescriptions for opioid naive patients and association with overdose and misuse: retrospective cohort study. Bmj, 2018. 360: p. j5790.

37. Breivik, H., B. Collett, V. Ventafridda, R. Cohen, and D. Gallacher. 2006. 'Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment', Eur J Pain, 10: 287-333.

38. Busse, J. W., L. Wang, M. Kamaleldin, S. Craigie, J. J. Riva, L. Montoya, S. M. Mulla, L. C. Lopes, N. Vogel, E. Chen, K. Kirmayr, K. De Oliveira, L. Olivieri, A. Kaushal, L. E. Chaparro, I. Oyberman, A. Agarwal, R. Couban, L. Tsoi, T. Lam, P. O. Vandvik, S. Hsu, M. M. Bala, S. Schandelmaier, A. Scheidecker, S. Ebrahim, V. Ashoorion, Y. Rehman, P. J. Hong, S. Ross, B. C. Johnston, R. Kunz, X. Sun, N. Buckley, D. I. Sessler, and G. H. Guyatt. 2018. 'Opioids for Chronic Noncancer Pain: A Systematic Review and Meta-analysis', *JAMA*, 320: 2448-60.

39. Campbell, G., S. Nielsen, B. Larance, R. Bruno, R. Mattick, W. Hall, N. Lintzeris, M. Cohen, K. Smith, and L. Degenhardt. 2015. 'Pharmaceutical Opioid Use and Dependence among People Living with Chronic Pain: Associations Observed within the Pain and Opioids in Treatment (POINT) Cohort', Pain Med, 16: 1745-58.

40. Campbell, James. 1996. 'APS 1995 Presidential Address', *J of Pain*, 5: 85-88.

41. Carmona-Bayonas, A., P. Jimenez-Fonseca, E. Castanon, A. Ramchandani-Vaswani, R. Sanchez-Bayona, A. Custodio, D. Calvo-Temprano, and J. A. Virizuela. 2017. 'Chronic opioid therapy in long-term cancer survivors', Clin Transl Oncol, 19: 236-50.

42. Carpenter, M. B. (1985). Core text of neuroanatomy. Baltimore, Williams & Wilkins.

43. Carroll, I., C.K. Wang, B.M. Wang, M.J. Gillespie, R. McCue, J.W. Younger, J. Trafton, K. Humphreys, S.B. Goodman, F. Dirbas, R.I. Whyte, J.S. Donington, W.B. Cannon, and S.C. Mackey. 2012. A pilot cohort study of the determinants of longitudinal opioid use after surgery, *Anesthesia and Analgesia* 115(3): 530-539

44. Caterina, M. J., M. A. Schumacher, M. Tominaga, T. A. Rosen, J. D. Levine, and D. Julius. 1997. 'The capsaicin receptor: a heat-activated ion channel in the pain pathway', Nature, 389: 816-24.

45. Celerier, E., et al. (2000). "Long-lasting hyperalgesia induced by fentanyl in rats: preventive effect of ketamine." Anesthesiology. 92(2): 465-472.

46. Centers for Disease Control and Prevention and National Center for Health Statistics, "Wide-ranging online data for epidemiologic research (WONDER)." (2018).

47. Centers for Disease Control and Prevention, "Annual Surveillance Report of Drug-Related Risks and Outcomes" (2017). https://www.cdc.gov/drugoverdose/pdf/pubs/2017-cdc-drug-surveillance-report.pdf.

48. Centers for Disease Control and Prevention, 2017. U.S. Opioid Prescribing Rate Maps https://www.cdc.gov/drugoverdose/maps/rxrate-maps.html

49. Centers for Disease Control and Prevention, "Prescribing opioid data" (2017). https://www.cdc.gov/drugoverdose/data/prescribing.html

50. Chan, F. J., A. M. Schwartz, J. Wong, C. Chen, B. Tiwari, and S. J. Kim. 2017. 'Use of Chronic Methadone Before Total Knee Arthroplasty', J Arthroplasty, 32: 2105-07.

51. Chaparro, LR. 'Opioids compared with placebo or other treatments for chronic low back pain: an update of the Cochrane Review', Spine (Phila Pa 1976), 39: 556-63. 2014

52. Chen, J. H., J. Hom, I. Richman, S. M. Asch, T. Podchiyska, and N. A. Johansen. 2016. 'Effect of opioid prescribing guidelines in primary care', Medicine (Baltimore), 95: e4760.

53. Cheng, D. and N.J.e. Majlesi, Emergency department opioid prescribing guidelines for the treatment of non-cancer related pain. 2013. 11: p. 21

54. Childers, J. W., L. A. King, and R. M. Arnold. 2015. 'Chronic Pain and Risk Factors for Opioid Misuse in a Palliative Care Clinic', Am J Hosp Palliat Care, 32: 654-9.

55. Chou, R., J. A. Turner, E. B. Devine, R. N. Hansen, S. D. Sullivan, I. Blazina, T. Dana, C. Bougatsos, and R. A. Deyo. 2015. 'The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop', Ann Intern Med, 162: 276-86.

56. Chou, R., J. C. Ballantyne, G. J. Fanciullo, P. G. Fine, and C. Miaskowski. 2009. 'Research gaps on use of opioids for chronic noncancer pain: findings from a review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline', J Pain, 10: 147-59.

57. Chu, Jason, et al., "New York City emergency department discharge opioid prescribing guidelines", New York City Department of Health and Mental Hygiene (2013).

58. Cicero, T. J., J. A. Inciardi, and A. Munoz. 2005. 'Trends in abuse of Oxycontin and other opioid analgesics in the United States: 2002-2004', *J Pain*, 6: 662-72.

59. Clauw, D. J. 2015. 'Diagnosing and treating chronic musculoskeletal pain based on the underlying mechanism(s)', Best Pract Res Clin Rheumatol, 29: 6-19.

60. Cole, J. M., et al. (2010). "Variability of transdermal fentanyl metabolism and excretion in pain patients." J Opioid Manag 6(1): 29-39.

61. Collins, J. J., et al. (1999). "Transdermal fentanyl in children with cancer pain: feasibility, tolerability, and pharmacokinetic correlates." J Pediatr 134(3): 319-323.

62. Comprehensive, National, and Cancer Network. 2016. 'Adult Cancer Pain: NCCN Clinical Practice Guidelines in Oncology'. https://www.nccn.org/professionals/physician_gls/pdf/pain.pdf.

63. Courtwright, David T. 2001. *Dark paradise: a history of opiate addiction in America* (Harvard University Press: Cambridge, Mass.).

64. Courtwright, David T. 2015. 'Preventing and Treating Narcotic Addiction — A Century of Federal Drug Control', 373: 2095-97.

65. Creyer E and Hrsistodoulakis I. Marketing pharmaceutical products to physicians: sales reps influence physicians' impressions of the industry. Marketing Health Services. 1998; 18(2): 34-38

66. Dahlhamer, J., et al. (2018). "Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults – United States, 2016." MMWR Morb Mortal Wkly Rep 67(36): 1001-1006.

67. Dahlhamer, J., J. Lucas, C. Zelaya, R. Nahin, S. Mackey, L. DeBar, R. Kerns, M. Von Korff, L. Porter, and C. Helmick. 2018. 'Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults - United States, 2016', *MMWR Morb Mortal Wkly Rep*, 67: 1001-06.

68. Dasgupta, N., M. J. Funk, S. Proescholdbell, A. Hirsch, K. M. Ribisl, and S. Marshall. 2016. 'Cohort Study of the Impact of High-Dose Opioid Analgesics on Overdose Mortality', Pain Med, 17: 85-98.

69. Davies, A., et al., Breakthrough cancer pain: an observational study of 1000 European oncology patients. J Pain Symptom Manage, 2013. 46(5): p. 619-28.

70. Datta A and Dave D. Effects of Physician-directed Pharmaceutical Promotion on Prescription Behaviors: Longitudinal Evidence. Health Economics. April 2017;26(4):450-469

71. de Hoogd, S., S. J. Ahlers, E. P. van Dongen, E. M. van de Garde, T. A. Hamilton-Ter Brake, A. Dahan, D. Tibboel, and C. A. Knibbe. 2016. 'Is Intraoperative Remifentanil Associated With Acute or Chronic Postoperative Pain After Prolonged Surgery? An Update of the Literature', Clin J Pain, 32: 726-35.

72. DEA. 2019. 'Controlled Substance Schedules', Diversion Control Division. https://www.deadiversion.usdoj.gov/schedules/.

73. Deandrea, S., G. Apolone, M. Montanari, and L. Moja. 2008. 'Prevalence of undertreatment in cancer pain. A review of published literature', Annals of Oncology, 19: 1985-91.

74. Delgado, M. K., Y. Huang, Z. Meisel, S. Hennessy, M. Yokell, D. Polsky, and J. Perrone. 2018. 'National Variation in Opioid Prescribing and Risk of Prolonged Use for Opioid-Naive Patients Treated in the Emergency Department for Ankle Sprains', Ann Emerg Med.

75. Denisco, R. C., G. A. Kenna, M. G. O'Neil, R. J. Kulich, P. A. Moore, W. T. Kane, N. R. Mehta, E. V. Hersh, and N. P. Katz. 2011. 'Prevention of prescription opioid abuse: the role of the dentist', J Am Dent Assoc, 142: 800-10.

76. Deyo, R. A., M. Von Korff, and D. Duhrkoop. 2015. 'Opioids for low back pain', BMJ, 350: g6380.

77. Dillie, K.S., Fleming, M.F., Mundt, M.P., French, M.T., Quality of life associated with daily opioid therapy in a primary care chronic pain sample. J Am Board Fam Med, 2008. 21(2): p. 108-117.

78. Donaldson, M., and J. H. Goodchild. 2010. 'Appropriate analgesic prescribing for the general dentist', Gen Dent, 58: 291-7; quiz 98-9.

79. Donovan, A. K., et al. (2016). "Faculty Communication Knowledge, Attitudes, and Skills Around Chronic Non-Malignant Pain Improve with Online Training." Pain Med 17(11): 1985-1992.

80. Doorenbos, A. Z., et al. (2013). "A blueprint of pain curriculum across prelicensure health sciences programs: one NIH Pain Consortium Center of Excellence in Pain Education (CoEPE) experience." J Pain 14(12): 1533-1538.

81. Dowell, D., et al. (2016). "CDC Guideline for Prescribing Opioids for Chronic Pain--United States, 2016." JAMA 315(15): 1624-1645.

82. Dunn, K. M., K. W. Saunders, C. M. Rutter, C. J. Banta-Green, J. O. Merrill, M. D. Sullivan, C. M. Weisner, M. J. Silverberg, C. I. Campbell, B. M. Psaty, and M. Von Korff. 2010. 'Opioid prescriptions for chronic pain and overdose: a cohort study', Ann Intern Med, 152: 85-92.

83. Dusetzina, S. B., et al. (2012). "Impact of FDA drug risk communications on health care utilization and health behaviors: a systematic review." Med Care 50(6): 466-478.

84. Dworkin, R. H., et al. (2007). "Pharmacologic management of neuropathic pain: evidence-based recommendations." Pain 132(3): 237-251.

85. Dworkin, R. H., et al. (2010). "Recommendations for the pharmacological management of neuropathic pain: an overview and literature update." Mayo Clinic proceedings. Mayo Clinic 85(3 Suppl): S3-14.

86. Dworkin, R. H., et al. (2011). "Considerations for extrapolating evidence of acute and chronic pain analgesic efficacy." Pain 152(8): 1705-1708.

87. Edlund, M. J., B. C. Martin, A. Devries, M. Y. Fan, J. B. Braden, and M. D. Sullivan. 2010. 'Trends in use of opioids for chronic noncancer pain among individuals with mental health and substance use disorders: the TROUP study', Clin J Pain, 26: 1-8.

88. Eilers, H., L. A. Philip, P. E. Bickler, W. R. McKay, and M. A. Schumacher. 2001. 'The reversal of fentanyl-induced tolerance by administration of "small-dose" ketamine', Anesth Analg, 93: 213-4.

89. Eisenach, J. C., C. Tong, and R. S. Curry. 2015. 'Failure of intrathecal ketorolac to reduce remifentanil-induced postinfusion hyperalgesia in humans', Pain, 156: 81-7.

90. Els, C., et al. (2017). "Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews." The Cochrane database of systematic reviews 10: CD012509.

91. Els, C., et al. (2017). "High-dose opioids for chronic non-cancer pain: an overview of Cochrane Reviews." The Cochrane database of systematic reviews 10: CD012299.

92. Eriksen, J., P. Sjogren, E. Bruera, O. Ekholm, and N.K. Rasmussen. 2006. 'Critical issues on opioids in chronic non-cancer pain. An epidemiological study.', Pain, 125: 172-9.

93. Fauber, J.J.M.T., Academics profit by making the case for opioid painkillers, 3 (2011).

94. Fauber, John, 'UW group ends firm funds', Milwaukee Journal Sentinel (2011).

95. FDA. 2017. "Timeline of selected FDA activities & significant events addressing opioid misuse & abuse."

96. Ferreira, S. H. and M. Nakamura (1979). "II - Prostaglandin hyperalgesia: the peripheral analgesic activity of morphine, enkephalins and opioid antagonists." Prostaglandins 18(2): 191-200.

97. Fields, H. L.Pain syndromes in neurology (Butterworths-Heinemann Ltd. 1990).

98. Finan, P. H. and B. Remeniuk "Is the brain reward system a mechanism of the association of sleep and pain?" Pain Manag. (2015).

99. Fine, P.G., A. Narayana, and S.D. Passik, Treatment of breakthrough pain with fentanyl buccal tablet in opioid-tolerant patients with chronic pain: appropriate patient selection and management. Pain Med, 2010. 11(7): p. 1024-36

100. Finnerup, N. B., et al. "Theevidence for pharmacological treatment of neuropathic pain."150(3) Pain.573, 581 (2010).

101. Fletcher, D., and V. Martinez. 2014. 'Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis', Br J Anaesth, 112: 991-1004.

102. Flor, H., T. Fydrich, and D. C. Turk. 1992. 'Efficacy of multidisciplinary pain treatment centers: a meta-analytic review', Pain, 49: 221-30.

103. Foley, Kathleen M. 1985. 'The Treatment of Cancer Pain', 313: 84-95.

104. Franklin, G. M., B. D. Stover, J. A. Turner, D. Fulton-Kehoe, and T. M. Wickizer. 2008. 'Early opioid prescription and subsequent disability among workers with back injuries: the Disability Risk Identification Study Cohort', Spine (Phila Pa 1976), 33: 199-204.

105. Franklin, G. M., E. A. Rahman, J. A. Turner, W. E. Daniell, and D. Fulton-Kehoe. 2009. 'Opioid use for chronic low back pain: A prospective, population-based study among injured workers in Washington state, 2002-2005', Clin J Pain, 25: 743-51.

106. Franklin, G. M., J. Mai, T. Wickizer, J. A. Turner, D. Fulton-Kehoe, and L. Grant. 2005. 'Opioid dosing trends and mortality in Washington State workers' compensation, 1996-2002', Am J Ind Med, 48: 91-9.

107. Frasco, P. E., J. Sprung, and T. L. Trentman. 2005. 'The impact of the joint commission for accreditation of healthcare organizations pain initiative on perioperative opiate consumption and recovery room length of stay', Anesth Analg, 100: 162-8.

108. Freburger, J. K., G. M. Holmes, R. P. Agans, A. M. Jackman, J. D. Darter, A. S. Wallace, L. D. Castel, W. D. Kalsbeek, and T. S. Carey. 2009. 'The rising prevalence of chronic low back pain', Arch Intern Med, 169: 251-8.

109. 'Fueling an epidemic. Exposing the financial ties between opioid manufacturers and third party advocacy groups'. 2018. US Senate and Homeland Security & Governmental Affairs Committee, Ranking Member's Office https://www.hsgac.senate.gov/imo/media/doc/REPORT-Fueling%20an%20Epidemic-Exposing%20the%20Financial%20Ties%20Between%20Opioid%20Manufacturers%20and%20Third%20Party%20Advocacy%20Groups.pdf accessed 4/11/2018.

110. Furlan, A., L. E. Chaparro, E. Irvin, and A. Mailis-Gagnon. 2011. 'A comparison between enriched and nonenriched enrollment randomized withdrawal trials of opioids for chronic noncancer pain', Pain Res Manag, 16: 337-51.

111. GAO. 2003. "Prescription Drugs: OxyContin Abuse and Diversion and Efforts to Address the Problem." In, edited by General Accounting Office.

112. Gaskell, H., S. Derry, C. Stannard, and R. A. Moore. 2016. 'Oxycodone for neuropathic pain in adults', Cochrane Database Syst Rev, 7: Cd010692.

113. Gaudreau, J. D., et al. (2007). "Opioid medications and longitudinal risk of delirium in hospitalized cancer\ patients." Cancer. 109(11): 2365-2373.}.

114. Geber, C., et al. (2013). "Pain in chemotherapy-induced neuropathy--more than neuropathic?" Pain 154(12): 2877-2887.

115. Geber, C., et al. (2013). "Response to letter by Werner et al." Pain 154(1): 176-178.

116. Gereau, R. W. t., et al. (2014). "A pain research agenda for the 21st century." J Pain 15(12): 1203-1214.

117. Gibbs, M. (2009). "The role of transdermal fentanyl patches in the effective management of cancer pain." Int J Palliat Nurs 15(7): 354-359.

118. Gimbel, J.S., Richards, P. & Portenoy, R.K. (2003). Controlled-release oxycodone for pain in diabetic neuropathy: A randomized controlled trial. Neurology, 60(6), 927-934.

119. Gisev, N., et al., Initiation of strong prescription opioids in Australia: cohort characteristics and factors associated with the type of opioid initiated. Br J Clin Pharmacol, 2016. 82(4): p. 1123-33.

120. Goldenbaum, D. M., et al. (2008). "Physicians charged with opioid analgesic-prescribing offenses." Pain Med 9(6): 737-747.

121. Goldenberg, D. L., D. J. Clauw, R. E. Palmer, and A. G. Clair. 2016. 'Opioid Use in Fibromyalgia: A Cautionary Tale', Mayo Clin Proc, 91: 640-8.

122. Gomes, T., M. M. Mamdani, I. A. Dhalla, J. M. Paterson, and D. N. Juurlink. 2011. 'Opioid dose and drug-related mortality in patients with nonmalignant pain', Arch Intern Med, 171: 686-91.

123. Gonul, F., Carter, F., Petrova, E., & Srinivasan, K. (2001). Promotion of prescription drugs and its impact on physicians' choice behavior. Journal of Marketing, 65, 79–90

124. Gourlay, G. K. (2001). "Treatment of cancer pain with transdermal fentanyl." Lancet Oncol 2(3): 165-172.

125. Gourlay, G. K., et al. (1989). "The transdermal administration of fentanyl in the treatment of postoperative pain: pharmacokinetics and pharmacodynamic effects." Pain 37(2): 193-202.

126. Gran, J.T., The epidemiology of chronic generalized musculoskeletal pain, Best Practice & Research Clinical Rheumatology, Volume 17, Issue 4,2003, Pages 547-561, https://doi.org/10.1016/S1521-6942(03)00042-1.

127. Grape, S., et al. (2010). "Formulations of fentanyl for the management of pain." Drugs 70(1): 57-72.

128. Greco, M. T., A. Roberto, O. Corli, S. Deandrea, E. Bandieri, S. Cavuto, and G. Apolone. 2014. 'Quality of cancer pain management: an update of a systematic

review of undertreatment of patients with cancer', Journal of clinical oncology: official journal of the American Society of Clinical Oncology, 32: 4149-54.

129. Grubb, B. D. (1998). "Peripheral and central mechanisms of pain." British Journal of Anaesthesia 81(1): 8-11.

130. Guzman, J., R. Esmail, K. Karjalainen, A. Malmivaara, E. Irvin, and C. Bombardier. 2001. 'Multidisciplinary rehabilitation for chronic low back pain: systematic review', BMJ, 322: 1511-6.

131. Haddox, J.D., D. Joranson, R.T. Angarola, A. Brady, D.B. Carr, R. Blonskey, D. Burchiel, M. Gitlin, M. Midcap, R. Payne, D. Simon, S. Vasudevan, and P. Wilson. 1997. 'The use of opioids for the treatment of chronic pain. A consensus statement from the American Academy of Pain Medicine and the American Pain Society', pub.: American Academy of Pain Medicine and American Pain Society.

132. Hadley, G., S. Derry, R. A. Moore, and P. J. Wiffen. 2013. 'Transdermal fentanyl for cancer pain',Cochrane Database of Systematic Reviews.

133. Hah, J.M., et al., "Factors associated with opioid use in a cohort of patients presenting for sugery", Pain Res. Treat. (2015).

134. Hale, M.E., K.L. Speight, Z. Harsanyi, T. Iwan, N.S. Slagle, P.G. Lacouture, and A.C. Darke. 1997. 'Efficacy of 12 hourly controlled-release codeine compared with as required dosing of acetaminophenplus codein in patients with chronic low back pain', Pain Res Manag, 2: 33-38.

135. Han, B., W. M. Compton, C. Blanco, E. Crane, J. Lee, and C. M. Jones. 2017. 'Prescription Opioid Use, Misuse, and Use Disorders in U.S. Adults: 2015 National Survey on Drug Use and Health', Ann Intern Med.

136. Harbaugh, C. M., J. S. Lee, K. P. Chua, B. Kenney, T. J. Iwashyna, M. J. Englesbe, C. M. Brummett, A. S. Bohnert, and J. F. Waljee. 2019. 'Association Between Long-term Opioid Use in Family Members and Persistent Opioid Use After Surgery Among Adolescents and Young Adults', JAMA Surg: e185838.

137. Hauser, W., F. Petzke, L. Radbruch, and T. R. Tolle. 2016. 'The opioid epidemic and the long-term opioid therapy for chronic noncancer pain revisited: a transatlantic perspective', Pain Manag, 6: 249-63.

138. Hayes, C.J., N. Payakachat, and C.J.Q.o.L.R. Li, Evaluation of opioid use among patients with back disorders and arthritis. 2018. 27(11): p. 3021-3035.

139. Hedegaard H, Miniño AM, Warner M. 2018. "Drug overdose deaths in the United States, 1999–2017." In NCHS Data Brief, edited by National Center for Health Statistics. Hyattsville, MD

140. Henschke, N., S. J. Kamper, and C. G. Maher. 2015. 'The epidemiology and economic consequences of pain', Mayo Clin Proc, 90: 139-47.

141. Hersh, E. V., S. Cooper, N. Betts, D. Wedell, K. MacAfee, P. Quinn, C. Lamp, G. Gaston, S. Bergman,and E. Henry. 1993. 'Single dose and multidose analgesic study of ibuprofen and meclofenamate sodium after third molar surgery', Oral Surg Oral Med Oral Pathol, 76: 680-7.

142. HHS. 2018. "Key substance use and mental health indicators in the United States: Results from the 2017 National Survey on Drug Use and Health", edited by Substance Abuse and Mental Health Services Administration. Rockville, MD: Center for Behavioral Health Statistics and Quality.

143. Hill, M. V., M. L. McMahon, R. S. Stucke, and R. J. Barth, Jr. 2017. 'Wide Variation and Excessive Dosage of Opioid Prescriptions for Common General Surgical Procedures', Ann Surg, 265: 709-14.

144. Hill, Maureen V., Ryland S. Stucke, Michelle L. McMahon, Julia L. Beeman, and Richard J. Jr. Barth. 2018. 'An Educational Intervention Decreases Opioid Prescribing After General Surgical Operations', 267: 468-72.

145. Hoffman, E. M., J. C. Watson, J. St Sauver, N. P. Staff, and C. J. Klein. 2017. 'Association of Long-term Opioid Therapy With Functional Status, Adverse Outcomes, and Mortality Among Patients With Polyneuropathy', JAMA Neurol, 74: 773-79.

146. Hoffman, DE. 2016. 'Treating pain V. Reducing drug diversion and abuse: Recalibrating the balance in our drug control laws and policies. ', *Saint Louis University Journal of Health Law & Policy*: 231-310.

147. Holliday, S. M., et al. (2017). "Does brief chronic pain management education change opioid prescribing rates? A pragmatic trial in Australian early-career general practitioners." Pain 158(2): 278-288.

148. Hoppe, J. A., et al. (2017). "Emergency Department Attending Physician Variation in Opioid Prescribing in Low Acuity Back Pain." West J Emerg Med 18(6): 1135-1142.

149. Howard, Ryan, Jennifer Waljee, Chad Brummett, Michael Englesbe, and Jay Lee. 2018. 'Reduction in Opioid Prescribing Through Evidence-Based Prescribing GuidelinesReduction in Opioid Prescribing Through Evidence-Based Prescribing GuidelinesLetters', JAMA Surg, 153: 285-87.

150. Hoy, D., et al. (2014). "The global burden of low back pain: estimates from the Global Burden of Disease 2010 study." Ann Rheum Dis 73(6): 968-974.

151. Hoy, S. M. and G. M. Keating (2008). "Fentanyl transdermal matrix patch (Durotep MT patch; Durogesic DTrans; Durogesic SMAT): in adults with cancer-related pain." Drugs 68(12): 1711-1721.

152. Huston P. Doctors want more industry-sponsored meetings. Medical Marketing & Media. 1993; 28(3): 48-53.

153. Hutchinson, M. R., et al. (2007). "Opioid-induced glial activation: mechanisms of activation and implications for opioid analgesia, dependence, and reward." ScientificWorldJournal 7: 98-111.

154. IMS Health, National Prescription Audit. 1997-2013. "Opioid Prescriptions Dispensed by US Retail Pharmacies, data extracted 2014.

155. Institute of America (2011). Relieving Pain in America. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington (DC).

156. Institute of Medicine Committee on Advancing Pain Research, Care, and Education, "Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research" (National Academies Press 2011).

157. Jamison, R.N., S.A. Raymond, E.A. Slawsby, S.S. Nedeljkovic, and N.P. Katz. 1998. 'Opioid therapy for chronic noncancer back pain: a randomized prospective study', Spine, 23: 2591-600.

158. Jin, M., T. Naumann, L. Regier, S. Bugden, M. Allen, L. Salach, K. Chelak, N. Blythe, A. Gagnon, and L. Dolovich. 2012. 'A brief overview of academic detailing in Canada: Another role for pharmacists', Can Pharm J (Ott), 145: 142-46.e2.

159. Jones, B. Summa Health eliminating opioids from surgeries. Akron Canton News. https://www.news5cleveland.com/news/local-news/akron-canton-news/summa-health-eliminating-opioids-from-surgeries

160. Kalso, E. (2004). "Biomarkers for pain." Pain 107(3): 199-201.

161. Kalso, E., et al., Opioids in chronic non-cancer pain: systematic review of efficacy and safety. Pain, 2004. 112(3): p. 372-80.

162. Kamper, S. J., A. T. Apeldoorn, A. Chiarotto, R. J. Smeets, R. W. Ostelo, J. Guzman, and M. W. van Tulder. 2015. 'Multidisciplinary biopsychosocial rehabilitation for chronic low back pain: Cochrane systematic review and meta-analysis', BMJ, 350: h444.

163. Kim SC, Landon JE, Solomon DH. *Clinical characteristics and medication uses among fibromyalgia patients newly prescribed amitriptyline, duloxetine, gabapentin, or pregabalin*. Arthritis Care & Research. 2013;65(11):1813–1819.

164. Kolodny, A., D. T. Courtwright, C. S. Hwang, P. Kreiner, J. L. Eadie, T. W. Clark, and G. C. Alexander. 2015. 'The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction', Annu Rev Public Health, 36: 559-74.

165. Koyama, T., et al. (2005). "The subjective experience of pain: where expectations become reality." Proc Natl Acad Sci U S A 102(36): 12950-12955.

166. Krashin, D., N. Murinova, and M. Sullivan. 2016. 'Challenges to Treatment of Chronic Pain and Addiction During the "Opioid Crisis"', Curr Pain Headache Rep, 20: 65.

167. Krebs, E. E., A. Gravely, S. Nugent, A. C. Jensen, B. DeRonne, E. S. Goldsmith, K. Kroenke, M. J. Bair, and S. Noorbaloochi. 2018. 'Effect of Opioid vs Nonopioid Medications on Pain-Related Function in Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain: The SPACE Randomized Clinical Trial', JAMA, 319: 872-82.

168. Krebs, E. E., et al. (2014). "Barriers to guideline-concordant opioid management in primary care--a qualitative study." J Pain 15(11): 1148-1155.

169. Kurita, G. P., and P. Sjogren. 2015. 'Pain management in cancer survivorship', Acta Oncol, 54: 629-34.

170. Lehmann, K. A. and D. Zech (1992). "Transdermal fentanyl: clinical pharmacology." J Pain Symptom Manage 7(3 Suppl): S8-16.

171. Leung, P. T. M., E. M. Macdonald, M. B. Stanbrook, I. A. Dhalla, and D. N. Juurlink. 2017. 'A 1980 Letter on the Risk of Opioid Addiction', N Engl J Med, 376: 2194-95.

172. Levine, J. D. (1998). "New directions in pain research: molecules to maladies." Neuron 20(4): 649-654.

173. Levine, J. D. and Y. O. Taiwo (1989). "Involvement of the mu-opiate receptor in peripheral analgesia." Neuroscience 32(3): 571-575.

174. Levine, Mark N., David L. Sackett, and Haydn Bush. 1986. 'Heroin vs Morphine for Cancer Pain?' Archives of internal medicine, 146: 353-56.

175. Levy, B., L. Paulozzi, K. A. Mack, and C. M. Jones. 2015. 'Trends in Opioid Analgesic-Prescribing Rates by Specialty, U.S., 2007-2012', Am J Prev Med, 49: 409-13.

176. Lin, D. H., E. Lucas, I. B. Murimi, A. Kolodny, and G. C. Alexander. 2017. 'Financial Conflicts of Interest and the Centers for Disease Control and Prevention's 2016 Guideline for Prescribing Opioids for Chronic Pain', JAMA Intern Med, 177: 427-28.

177. Linssen, A. C., and P. Spinhoven. 1992. 'Multimodal treatment programmes for chronic pain: a quantitative analysis of existing research data', J Psychosom Res, 36: 275-86.

178. Lucas, Charles E, Angie L Vlahos, and Anna M. Ledgerwood. Journal of the American College of Surgeons Ledgerwood. 2007. 'Kindness kills: the negative impact of pain as the fifth vital sign', 205: 101-07.

179. Macdougal, J. R. (1955). "Prescribing." Can Med Assoc J 73(12): 991.

180. Machelska, H. and C. Stein (2000). "Pain control by immune-derived opioids." Clinical and Experimental Pharmacology and Physiology 27(7): 533-536.

181. Mack, J. Pharma Marketing News. Pharma Promotional Spending in 2013. http://www.pharma-mkting.com/news/pmnews1305-article01.pdf Accessed August 13, 2018

182. Maier, C., J./Klinger Hildebrandt, R., C. Henrich-Eberl, and G. Lindena. 2002. 'Morphine responsiveness, efficacy and tolerability in patients with chronic non-tumor associated pain - results of a double-blind placebo-controlled trial (MONTAS)', Pain, 97: 223-33.

183. Mark, Jaron, Deanna M. Argentieri, Camille A. Gutierrez, Kayla Morrell, Kevin Eng, Alan D. Hutson, Paul Mayor, J. Brian Szender, Kristen Starbuck, Sarah Lynam, Bonnie Blum, Stacey Akers, Shashikant Lele, Gyorgy Paragh, Kunle Odunsi, Oscar de Leon-Casasola, Peter J. Frederick, and Emese Zsiros. 2018. 'Ultrarestrictive Opioid Prescription Protocol for Pain Management',JAMA Network Open, 1: e185452-e52.

184. Marks, R. M., and E. J. Sachar. 1973. 'Undertreatment of medical inpatients with narcotic analgesics', Ann Intern Med, 78: 173-81.

185. Maughan, B. C., M. A. Bachhuber, N. Mitra, and J. L. Starrels. 2015. 'Prescription monitoring programs and emergency department visits involving opioids, 2004-2011', Drug Alcohol Depend, 156: 282-88.

186. McCarberg, B.H., The treatment of breakthrough pain. Pain Med, 2007. 8 Suppl 1: p. S8-13.

187. McNicol, E. D., A. Midbari, and E. Eisenberg. 2013. 'Opioids for neuropathic pain', Cochrane Database Syst Rev: Cd006146.

188. Meldrum, M. L. 2003. 'A capsule history of pain management', JAMA, 290: 2470-5. ———. 2016. 'The Ongoing Opioid Prescription Epidemic: Historical Context', Am J Public Health, 106: 1365-6.

189. Mercadante, S., et al., Italian Oncological Pain Survey (IOPS): a multicentre Italian study of breakthrough pain performed in different settings. Clin J Pain, 2015. 31(3): p. 214-21.

190. Meske, D. S., O. D. Lawal, H. Elder, V. Langberg, F. Paillard, and N. Katz. 2018. 'Efficacy of opioids versus placebo in chronic pain: a systematic review and meta-analysis of enriched enrollment randomized withdrawal trials', J Pain Res, 11: 923-34.

191. Mezei, L., and B. B. Murinson. 2011. 'Pain education in North American medical schools', *J Pain*, 12: 1199-208.

192. Mitchell, A. and H. S. Smith (2010). "Applying partially occluded fentanyl transdermal patches to manage pain in pediatric patients." J Opioid Manag 6(4): 290-294.

193. Moore, P. A., H. S. Nahouraii, J. G. Zovko, and S. R. Wisniewski. 2006. 'Dental therapeutic practice patterns in the U.S. II. Analgesics, corticosteroids, and antibiotics', Gen Dent, 54: 201-7; quiz 08, 21-2.

194. Moore, R. A., P. J. Wiffen, S. Derry, T. Maguire, Y. M. Roy, and L. Tyrrell. 2015. 'Non-prescription (OTC) oral analgesics for acute pain - an overview of Cochrane reviews', Cochrane Database Syst Rev: Cd010794.

195. Morasco, B.J., et al., "Clinical characteristics of veterans prescribed high doses of opioid medications for chronic non-caner pain", 151(3) Pain 625, 632 (2010).

196. Morgan, JP. 1985. "American opiophobia: customary underutilization of opioid analgesics." In, 163-73. Adv Alcohol Subst Abuse.

197. Morita, T., et al. (2005). "Opioid rotation from morphine to fentanyl in delirious cancer patients: an\ open-label trial." J Pain Symptom Manage. 30(1): 96-103.}.

198. Mosher, H. J., L. Jiang, M. S. Vaughan Sarrazin, P. Cram, P. J. Kaboli, and M. W. Vander Weg. 2014. 'Prevalence and characteristics of hospitalized adults on chronic opioid therapy', J Hosp Med, 9: 82-7.

199. Mudumbai, S. C., E. M. Oliva, E. T. Lewis, J. Trafton, D. Posner, E. R. Mariano, R. S. Stafford, T. Wagner, and J. D. Clark. 2016. 'Time-to-Cessation of Postoperative Opioids: A Population-Level Analysis of the Veterans Affairs Health Care System', Pain Med, 17: 1732-43.

200. Mularski, R. A., F. White-Chu, D. Overbay, L. Miller, S. M. Asch, and L. Ganzini. 2006. 'Measuring pain as the 5th vital sign does not improve quality of pain management', J Gen Intern Med, 21: 607-12.

201. Munglani, R. 2019. 'The not so vital sign or why there is no stethoscope for pain', Pain News, 17: 4-7.

202. Murshid Ali M, Mohaidin Z. Models and theories of prescribing decisions: A review and suggested a new model. Pharmacy Practice 2017 Apr-Jun;15(2):990

203. Musto, David F. 1999. The American disease: origins of narcotic control (Oxford University Press: New York).

204. Nahin, R. L. (2015). "Estimates of pain prevalence and severity in adults: United States, 2012." J Pain 16(8): 769-780.

205. Nelson, L. and R. Schwaner (2009). "Transdermal fentanyl: pharmacology and toxicology." J Med Toxicol 5(4): 230-241.

206. Nelson, L. S. and J. Perrone (2012). "Curbing the opioid epidemic in the United States: the risk evaluation and mitigation strategy (REMS)." JAMA 308(5): 457-458.

207. Noyes, M. and H. Irving (2001). "The use of transdermal fentanyl in pediatric oncology palliative care." Am J Hosp Palliat Care 18(6): 411-416.

208. O'Brien, M. A., S. Rogers, G. Jamtvedt, A. D. Oxman, J. Odgaard-Jensen, D. T. Kristoffersen, L. Forsetlund, D. Bainbridge, N. Freemantle, D. A. Davis, R. B. Haynes, and E. L. Harvey. 2007. 'Educational outreach visits: effects on professional practice and health care outcomes', Cochrane Database Syst Rev: Cd000409.

209. O'Connor, A. B. and R. H. Dworkin (2009). "Treatment of neuropathic pain: an overview of recent guidelines." Am J Med. 122(10 Suppl): S22-32.

210. Okie, S. "A Flood of Opioids, a Rising Tide of Deaths" N Engl J Med 2010; 363:1981-1985, 2010.

211. Okunseri, Christopher, Elaye Okunseri, Qun Xiang, Joshua M. Thorpe, and Aniko Szabo. 2014. 'Prescription of opioid and nonopioid analgesics for dental care in emergency departments: Findings from the National Hospital Ambulatory Medical Care Survey', 74: 283-92.

212. Olfson, M., S. Wang, M. Iza, S. Crystal, and C. Blanco. 2013. 'National trends in the office-based prescription of schedule II opioids', *J Clin Psychiatry*, 74: 932-9.

213. O'Neil, M., and K. L. Hannah. 2010. 'Understanding the cultures of prescription drug abuse, misuse, addiction, and diversion', W V Med J, 106: 64-70.

214. British Pain Society, 'Opioids for persistent pain: summary of guidance on good practice from the British Pain Society'. 2012. Br J Pain, 6: 9-10.

215. Paice, J. A., R. Portenoy, C. Lacchetti, T. Campbell, A. Cheville, M. Citron, L. S. Constine, A. Cooper, P. Glare, F. Keefe, L. Koyyalagunta, M. Levy, C. Miaskowski, S. Otis-Green, P. Sloan, and E. Bruera. 2016. Management of

Chronic Pain in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline', J Clin Oncol, 34: 3325-45.

216. Pan, G. 2016. "Challenges in assessing real world use and abuse of pain medicines." In, edited by FDA Science Board Meeting.

217. Paone, D., D. Dowell, and D. Heller, Preventing misuse of prescription opioid drugs. City Health Information http://www.nyc.gov/html/doh/downloads/pdf/chi/chi30-4.pdf, 2011. 30(4): p. 23-30.

218. Patijn, J, JM de Rijke, MHJ van den Beuken-van Everdingen, AG Kessels, HC Schouten, and M van Kleef. 2007. 'Prevalence of pain in patients with cancer: a systematic review of the past 40 years', Annals of Oncology, 18: 1437-49.

219. Patrick, L. E., E. M. Altmaier, and E. M. Found. 2004. 'Long-term outcomes in multidisciplinary treatment of chronic low back pain: results of a 13-year follow-up', Spine, 29: 850-5.

220. Paulozzi, L. J., E. M. Kilbourne, N. G. Shah, K. B. Nolte, H. A. Desai, M. G. Landen, W. Harvey, and L. D. Loring. 2012. 'A history of being prescribed controlled substances and risk of drug overdose death', Pain Med, 13: 87-95.

221. Pedersen, L., P. C. Borchgrevink, Riphagen, II, and O. M. Fredheim. 2014. 'Long- or short-acting opioids for chronic non-malignant pain? A qualitative systematic review', Acta Anaesthesiol Scand, 58: 390-401.

222. Pergolizzi, J., et al. (2008). "Opioids and the management of chronic severe pain in the elderly: consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone)." Pain Pract 8(4): 287-313.

223. Physicians, A.C.o.E., Maryland emergency department and acute care facility guidelines for prescribing opioids. Baltimore, MD: Maryland Chapter, American College of Emergency Physicians; 2014.

224. Plezia, P. M., et al. (1989). "Transdermal fentanyl: pharmacokinetics and preliminary clinical evaluation." Pharmacotherapy 9(1): 2-9.

225. del Portal, D. A., M. E. Healy, W. A. Satz, and R. M. McNamara. 2016. 'Impact of an Opioid Prescribing Guideline in the Acute Care Setting', J Emerg Med, 50: 21-7.

226. Portenoy, R. K., J. T. Farrar, M. M. Backonja, C. S. Cleeland, K. Yang, M. Friedman, S. V. Colucci, and P. Richards. 2007. 'Long-term use of controlled-release oxycodone for noncancer pain: results of a 3-year registry study', Clin J Pain, 23: 287-99.

227. Portenoy, R. K., and K. M. Foley. 1986. 'Chronic use of opioid analgesics in non-malignant pain: report of 38 cases', Pain, 25: 171-86.

228. Portenoy, R. K., D. E. Moulin, A. Rogers, C. E. Inturrisi, and K. M. Foley. 1986. 'I.V. infusion of opioids for cancer pain: clinical review and guidelines for use', Cancer treatment reports, 70: 575-81.

229. Portenoy, R. K., et al. (1993). "Transdermal fentanyl for cancer pain. Repeated dose pharmacokinetics." Anesthesiology 78(1): 36-43.

230. Portenoy, R.K. and N.A. Hagen, Breakthrough pain: definition, prevalence and characteristics. Pain, 1990. 41(3): p. 273-81.

231. Portenoy, R.K., et al., Fentanyl buccal tablet (FBT) for relief of breakthrough pain in opioid-treated patients with chronic low back pain: a randomized, placebo-controlled study. Curr Med Res Opin, 2007. 23(1): p. 223-33.

232. Portenoy, R.K., et al., Prevalence and characteristics of breakthrough pain in opioid-treated patients with chronic noncancer pain. J Pain, 2006. 7(8): p. 583-91.

233. Porter, J., and H. Jick. 1980. 'Addiction rare in patients treated with narcotics (letter)', N Engl J Med, 302: 123.

234. Practice guidelines for chronic pain management: an updated report by the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine." Anesthesiology 112(4): 810-833. (2010).

235. Qaseem, A., T. J. Wilt, R. M. McLean, and M. A. Forciea. 2017. 'Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians', Ann Intern Med, 166: 514-30.

236. Drugs of Dependence Unit, 'Quick Clinical Guideline for the use of Opioids in Non-Malignant Pain', Government of Western Australia, Drug and Alcohol Office (2010). https://www.health.qld.gov.au/__data/assets/pdf_file/0032/374693/ddu_quick_guide.pdf.

237. Rapp, S.E., L.B. Ready, and M.L. Nessly. 1995. 'Acute pain management in patients with prior opioid consumption: a case-controlled retrospective review', Pain, 61: 195-201.

238. Rasubala, L., L. Pernapati, X. Velasquez, J. Burk, and Y. F. Ren. 2015. 'Impact of a Mandatory Prescription Drug Monitoring Program on Prescription of Opioid Analgesics by Dentists', PLoS One, 10: e0135957.

239. Raymond, B. and I. Morawiecka (2004). "Transdermal fentanyl (Duragesic): respiratory arrest in adolescents." CMAJ 171(8): 991-992.

240. Remillard, D., A. D. Kaye, and H. McAnally. 2019. 'Oxycodone's Unparalleled Addictive Potential: Is it Time for a Moratorium?' *Curr Pain Headache Rep*, 23: 15.

241. Ren, Z. Y., J. Shi, D. H. Epstein, J. Wang, and L. Lu. 2009. 'Abnormal pain response in pain-sensitive opiate addicts after prolonged abstinence predicts increased drug craving', Psychopharmacology (Berl), 204: 423-9.

242. Richebe, P., M. Julien, and V. Brulotte. 2015. 'Potential strategies for preventing chronic postoperative pain: a practical approach: Continuing Professional Development', Can J Anaesth, 62: 1329-41.

243. Roberts, A. H., R. A. Sternbach, and J. Polich. 1993. 'Behavioral management of chronic pain and excess disability: long-term follow-up of an outpatient program', The Clinical journal of pain, 9: 41-8.

244. Roth, S. H., R. M. Fleischmann, F. X. Burch, F. Dietz, B. Bockow, R. J. Rapoport, J. Rutstein, and P. G. Lacouture. 2000. 'Around-the-clock, controlled-release oxycodone therapy for osteoarthritis-related pain: placebo-controlled trial and long-term evaluation', Arch Intern Med, 160: 853-60.

245. Rudd, R. A., P. Seth, F. David, and L. Scholl. 2016. 'Increases in Drug and Opioid-Involved Overdose Deaths - United States, 2010-2015', *MMWR Morb Mortal Wkly Rep*, 65: 1445-52.

246. Sandler, A. N., et al. (1994). "A double-blind, placebo-controlled trial of transdermal fentanyl after abdominal hysterectomy. Analgesic, respiratory, and pharmacokinetic effects." Anesthesiology 81(5): 1169-1180; discussion 1126A.

247. Saper, J. R., and A. E. Lake, 3rd. 2008. 'Continuous opioid therapy (COT) is rarely advisable for refractory chronic daily headache: limited efficacy, risks, and proposed guidelines', Headache, 48: 838-49.

248. Sasson, M. and P. Shvartzman (2006). "Fentanyl patch sufficient analgesia for only one day." J Pain Symptom Manage 31(5): 389-391.

249. Schatman, ME. 2010. 'Interdisciplinary chronic pain management: perspectives on history, current status, and future viability.' in J Ballantyne SM Fishman, J Rathmell (ed.), *Bonica's Management of Pain.* (Lippincott Williams & Wilkins: Baltimore, MD).

250. Schiltenwolf, M., M. Akbar, A. Hug, U. Pfuller, S. Gantz, E. Neubauer, H. Flor, and H. Wang. 2014. 'Evidence of specific cognitive deficits in patients with chronic low back pain under long-term substitution treatment of opioids', Pain Physician, 17: 9-20.

251. Schmidt-Hansen, M., M. I. Bennett, S. Arnold, N. Bromham, and J. S. Hilgart. 2015. 'Oxycodone for cancer-related pain', Cochrane Database Syst Rev: Cd003870.

252. Schroeder, Alan R., Melody Dehghan, Thomas B. Newman, Jason P. Bentley, and K. T. Park. 2019. 'Association of Opioid Prescriptions From Dental Clinicians for US Adolescents and Young Adults With Subsequent Opioid Use and AbuseDental Clinician–Prescribed Opioids for Adolescents and Young Adults and Subsequent Substance AbuseDental Clinician–Prescribed Opioids for Adolescents and Young Adults and Subsequent Substance Abuse', JAMA Intern Med, 179: 145-52.

253. Scholl, L., Seth P., Kariisa M., Wilson N., and Baldwin G. 2018. "Drug and Opioid-Involved Overdose Deaths – United States, 2013-2017." In.: Morb Mortal Wkly Rep. ePub.

254. Scully, R. E., A. J. Schoenfeld, W. Jiang, S. Lipsitz, M. A. Chaudhary, P. A. Learn, T. Koehlmoos, A. H. Haider, and L. L. Nguyen. 2018. 'Defining Optimal Length of Opioid Pain Medication Prescription After Common Surgical Procedures', JAMA Surg, 153: 37-43.

255. Seth, Puja, Rose A. Rudd, Rita K. Noonan, and Tamara M. Haegerich. 2018. 'Quantifying the Epidemic of Prescription Opioid Overdose Deaths', 108: 500-02.

256. Shah, A., C.J. Hayes, and B.C. Martin, Characteristics of initial prescription episodes and likelihood of long-term opioid use - United States, 2006-2015. MMWR Morb Mortal Wkly Rep, 2017. 66: p. 265-269.

257. Sheehan, Kayla, Jessica Lee, Jillian Chong, Kathryn Zavala, Manohar Sharma, Sjaak Philipsen, Tomoyuki Maruyama, Zheyun Xu, Zhonghui Guan, Helge Eilers, Tomoyuki Kawamata, and Mark Schumacher. 2019. 'Transcription factor Sp4 is required for hyperalgesic state persistence', *PLoS One*, 14: e0211349.

258. Shindo, et al., "Comparison of Opioid Utilization Patterns after Major Head and Neck Procedures between Hong Kong and the United States," JAMA Otolaryngology E1, E6 (2018).

259. Shindo, M., J. Lim, E. Leon, L. Moneta, R. Li, and L. Quintinalla-Diek. 'Opioid Prescribing Practice and Needs in Thyroid and Parathyroid Surgery', JAMA Otolaryngol Head Neck Surg. (2018).

260. Sjogren, P., Epidemiology of chronic pain and critical issues on opioid use. Pain, 2011. 152(6): p. 1219-20.

261. Sjogren, P., M. Gronbaek, V. Peuckmann, and O. Ekholm. 2010. 'A population-based cohort study on chronic pain: the role of opioids', Clin J Pain, 26: 763-9.

262. Sluka, K. A., and D. J. Clauw. 2016. 'Neurobiology of fibromyalgia and chronic widespread pain', Neuroscience.

263. Soumerai, S. B., and J. Avorn. 1987. 'Predictors of physician prescribing change in an educational experiment to improve medication use', Med Care, 25: 210-21.

264. Soumerai, S. B., and J. Avorn. 1990. 'Principles of educational outreach ('academic detailing') to improve clinical decision making', JAMA, 263: 549-56.

265. Stros M and Lee N. Marketing dimensions in the prescription pharmaceutical industry: a systematic literature review. J of Strategic Marketing 2015; 23(4):318-336.

266. Sun, E. C., B. D. Darnall, L. C. Baker, and S. Mackey. 2016. 'Incidence of and Risk Factors for Chronic Opioid Use Among Opioid-Naive Patients in the Postoperative Period', JAMA Intern Med, 176: 1286-93.

267. Tan, P. D., J. S. Barclay, and L. J. Blackhall. 2015. 'Do Palliative Care Clinics Screen for Substance Abuse and Diversion? Results of a National Survey', J Palliat Med, 18: 752-7.

268. The Canadian National Pain Center, 'The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain' (2017). *http://nationalpaincentre.mcmaster.ca/documents/Opioid%20GL%20for%20CMAJ_01may2017.pdf*

269. Thorson, D., et al., Acute pain assessment and opioid prescribing protocol, Institute for Clinical Systems Improvement (2014).

270. Toblin, R.L., et al., A population-based survey of chronic pain and its treatment with prescription drugs. Pain, 2011. 152(6): p. 1249-55.

271. Tompkins, D. A., J. G. Hobelmann, and P. Compton. 2017. 'Providing chronic pain management in the "Fifth Vital Sign" Era: Historical and treatment perspectives on a modern-day medical dilemma', Drug Alcohol Depend, 173 Suppl 1: S11-s21.

272. Trang, T., R. Al-Hasani, D. Salvemini, M. W. Salter, H. Gutstein, and C. M. Cahill. 2015. 'Pain and Poppies: The Good, the Bad, and the Ugly of Opioid Analgesics', J Neurosci, 35: 13879-88.

273. Turk, D. C. 2002. 'Clinical effectiveness and cost-effectiveness of treatments for patients with chronic pain', Clin J Pain, 18: 355-65.

274. Turk, Dennis C., and Akiko Okifuji. 1998. 'Treatment of Chronic Pain Patients: Clinical Outcomes, Cost-Effectiveness, and Cost-Benefits of Multidisciplinary Pain Centers', 10: 181-208.

275. Van Hoof, T. J., and T. P. Meehan. 2012. 'Using theory and evidence to guide the use of educational outreach to improve patient care', Am J Med Qual, 27: 467-71.

276. Van Lersberghe, C., et al. (1994). "Continuous administration of fentanyl for postoperative pain: a comparison of the epidural, intravenous, and transdermal routes." J Clin Anesth 6(4): 308-314.

277. Van Nimmen, N. F., et al. (2010). "Fentanyl transdermal absorption linked to pharmacokinetic characteristics in patients undergoing palliative care." J Clin Pharmacol 50(6): 667-678.

278. Van Zee, A. 2009. 'The promotion and marketing of oxycontin: commercial triumph, public health tragedy', Am J Public Health, 99: 221-7.

279. VanDenKerkhof, E. G., W. M. Hopman, D. H. Goldstein, R. A. Wilson, T. E. Towheed, M. Lam, M. B. Harrison, M. L. Reitsma, S. L. Johnston, J. D. Medd, and I. Gilron. 2012. 'Impact of perioperative pain intensity, pain qualities, and opioid use on chronic pain after surgery: a prospective cohort study', Reg Anesth Pain Med, 37: 19-27.

280. Vander Weele, C. M., K. A. Porter-Stransky, O. S. Mabrouk, V. Lovic, B. F. Singer, R. T. Kennedy, and B. J. Aragona. 2014. 'Rapid dopamine transmission within the nucleus accumbens: dramatic difference between morphine and oxycodone delivery', *Eur J Neurosci*, 40: 3041-54.

281. Veliz, P., Q. Epstein-Ngo, E. Austic, C. Boyd, and S. E. McCabe. 2015. 'Opioid use among interscholastic sports participants: an exploratory study from a sample of college students', Res Q Exerc Sport, 86: 205-11.

282. Vincent, A. Lahr, B. D., Wolfe, F., Clauw, D. J., Whipple, M. O., Oh, T. H., Barton, D. L. and St. Sauver, J. (2013), Prevalence of Fibromyalgia: A Population‐Based Study in Olmsted County, Minnesota, Utilizing the Rochester Epidemiology Project. Arthritis Care Res, 65: 786-792. doi:10.1002/acr.21896

283. 'Vital signs: overdoses of prescription opioid pain relievers - United States, 1999-2008'. 2011. *Morbidity and Mortality Weekly Report (MMWR) www.cdc.gov/mmwr/preview/mmwrhtml/mm6043a4.htm*.

284. Volkow, N. D. and A. T. McLellan (2016). "Mitigation Strategies for Opioid Abuse." N Engl J Med 375(1): 96.

285. Volkow, N. D. and A. T. McLellan (2016). "Opioid Abuse in Chronic Pain--Misconceptions and Mitigation Strategies." N Engl J Med 374(13): 1253-1263.

286. Von Korff, M., et al. (2016). "United States National Pain Strategy for Population Research: Concepts, Definitions, and Pilot Data." J Pain 17(10): 1068-1080.

287. Von Korff, Michael. 2013. 'Opioids for chronic musculoskeletal pain: Putting patient safety first', 154: 2583-85.

288. Vowles, K. E., M. L. McEntee, P. S. Julnes, T. Frohe, J. P. Ney, and D. N. van der Goes. 2015. 'Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis', Pain, 156: 569-76.

289. Weiland, B. M., A. G. Wach, B. P. Kanar, M. T. Castele, M. F. Sosovicka, M. R. Cooke, and P. A. Moore. 2015. 'Use of opioid pain relievers following extraction of third molars', Compend Contin Educ Dent, 36: 107-11; quiz 12, 14.

290. Wheeler, E., et al. (2015). "Opioid Overdose Prevention Programs Providing Naloxone to Laypersons - United States, 2014." MMWR Morb Mortal Wkly Rep 64(23): 631-635.

291. WHO. Cancer Pain Relief. Geneva: *World Health Organization*, Expert Committee on Cancer Pain Relief and Active Supportive Care, Geneva.

292. Wiffen, P. J., B. Wee, and R. A. Moore. 2016. 'Oral morphine for cancer pain', Cochrane Database of Systematic Reviews.

293. Yi, P., and P. Pryzbylkowski. 2015. 'Opioid Induced Hyperalgesia', Pain Med, 16 Suppl 1: S32-6.

294. Zedler, B., L. Xie, L. Wang, A. Joyce, C. Vick, F. Kariburyo, P. Rajan, O. Baser, and L. Murrelle. 2014. 'Risk Factors for Serious Prescription Opioid-Related Toxicity or Overdose among Veterans Health Administration Patients', Pain Med.

295. Zenz, M., and A. Willweber-Strumpf. 1993. 'Opiophobia and cancer pain in Europe', Lancet, 341: 1075-6.

296. Zeppetella, G., and A. N. Davies. 2013. 'Opioids for the management of breakthrough pain in cancer patients', Cochrane Database Syst Rev: Cd004311.

297. Zernikow, B., et al. (2007). "Transdermal fentanyl in childhood and adolescence: a comprehensive literature review." J Pain 8(3): 187-207.

298. Zernikow, B., et al. (2009). "Pediatric palliative care: use of opioids for the management of pain." Paediatr Drugs 11(2): 129-151.

299. Zwisler, S. T., J. Hallas, M. S. Larsen, G. Handberg, S. Mikkelsen, and T. P. Enggaard. 2015. 'Opioid prescriptions before and after high-energy trauma', J Opioid Manag, 11: 313-8.

300. Zywiel, M. G., D. A. Stroh, S. Y. Lee, P. M. Bonutti, and M. A. Mont. 2011. 'Chronic opioid use prior to total knee arthroplasty', J Bone Joint Surg Am, 93: 1988-93.

BATES STAMPED DOCUMENTS

301. ACTAVIS00006930

302. ACTAVIS0795954

303. ALLERGAN_MDL_00001525

304. ALLERGAN_MDL_00020454

305. ALLERGAN_MDL_01052119

306. ALLERGAN_MDL_02513506

307. CHI_000435580

308. County Wayne Exh 33 - Policymaker's Guide to Understanding Pain_American Pain Foundation 2011 (Dkt # 1-33, *County of Wayne, et al. v. Purdue Pharma L.P., et al.*, No. 17-cv-13334 (E.D. MI))

309. Defeat Chronic Pain Now! pgs 176-178

310. END00246672

311. END00366720

312. ENDO-CHI_LIT-00024520

313. ENDO-CHI_LIT-00084049

314. ENDO-CHI_LIT-00208241

315. ENDO-OPIOID_MDL-00545087

316. ENDO-OPIOID_MDL-00678060

317. ENDO-OPIOID_MDL-00678171

318. ENDO-OPIOID_MDL-01761737

319. ENDO-OPIOID_MDL-02002555

320. ENDO-OPIOID_MDL-04908072

321. ENDO-OR-CID-00915135

322. INSYS-MDL-000370027

323. JAN00222151

324. JAN00222296

325. JAN-MS-00016372

326. JAN-MS-00299212

327. JAN-MS-00303825

328. JAN-MS-00306286

329. JAN-MS-00310473

330. JAN-MS-00386085

331. JAN-MS-00476773

332. JAN-MS-00508566

333. JAN-MS-00653403

334. JAN-MS-00653426

335. JAN-MS-00890573

336. JAN-MS-00930135

337. JAN-MS-02474819

338. JAN-MS-02757939

339. JAN-MS-03090578

340. JAN-MS-03090610

341. JAN-OH-00000004

342. KP360_OHIOMDL_000027041

343. MNK-T1_0001161164

344. MNK-T1_0001161191

345. MNK-T1_0001161192

346. MNK-T1_0001161234

347. MNK-T1_0002157893

348. MNK-T1_0002232762

349. PDD1501605477

350. PDD1501614879

351. PDD1502305933

352. PDD1701006198

353. PDD1701006263

354. PDD1701345999

355. PDD1712900035

356. PDD1712900035

357. PDD9316728354

358. PDD9520404001

359. PDD8013004694

360. PKY180112501

361. PKY180117076

362. PKY180121679

363. PKY180252074

364. PKY180261022

365. PKY180544129

366. PKY180544556

367. PKY180544557

368. PKY180989588

369. PKY181004480

370. PKY181004511

371. PKY181004545

372. PKY181312103

373. PKY181386644

374. PKY181823986

375. PKY181949492

376. PKY182142182

377. PKY182832534

378. PKY182895039

379. PLLPC009000025991

380. PPLP003996830

381. PPLP003998219

382. PPLP004030121

383. PPLP004030136

384. PPLP004030150

385. PPLP004030154

386. PPLP004030214

387. PPLP004030223

388. PPLP004030366

389. PPLP004030463

390. PPLP004031668

391. PPLP004032323

392. PPLP004032436

393. PPLPC017000008947

394. PPLPC009000025992

395. PPLPC009000026013

396. PPLPC018001290131

397. PPLPC023000857325

398. PPLPC031001394870

399. PPLPC031001394872

400. PPLPMDL0080000001

401. PURCHI-000622957

402. PURCHI-000622986

403. PURCHI-000674082

404. SHC-000001965

405. SHC-000004120

406. SHC-000008102

407. SHC-000008118

408. SHC-000020630

409. SHC-000026038

410. SHC-000026456

411. SHC-000026573

412. SHC-000001965

413. SHC-000004120

414. SHC-000008102

415. SHC-000008118

416. SHC-000026456